



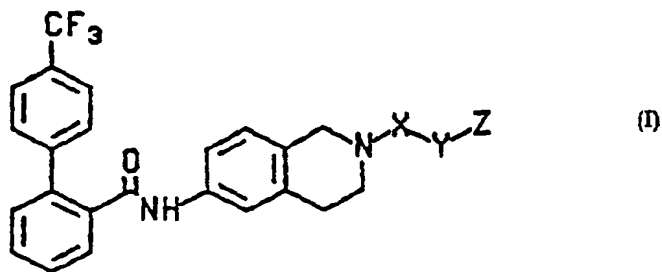
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 217/04, 217/06, 405/06, 413/06, 409/06, 401/06, 417/06, 217/08, 401/10, C07C 233/75, C07D 217/02, C07C 205/19, 215/68, A61K 31/47, 31/495	A1	(11) International Publication Number: WO 96/40640 (43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/IB95/00448 (22) International Filing Date: 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHANG, George [US/US]; 1 Winthrop Hill Road, Ivoryton, CT 06442 (US). DORFF, Peter, H. [US/US]; 63 Janice Lane, Norwich, CT 06360 (US). QUALLICH, George, J. [US/US]; 349 Norwich Westerly Road, North Stonington, CT 06359 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: CA, FI, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. With amended claims.

(54) Title: BIPHENYL-2-CARBOXYLIC ACID-TETRAHYDRO-ISOQUINOLIN-6-YL AMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND/OR APOLIPOPROTEIN B (Apo B) SECRETION

(57) Abstract

Compounds of formula (I), wherein X is CH₂, CO, CS or SO₂; Y is selected from: a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be mono-substituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl, NH, and O, provided that if X is CH₂, Y is a direct link; Z is selected from the following groups: (1) H, halo, cyano,



(2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl, (3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH, (4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl, (5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy, (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH₂, Z is H or is selected from groups (4) and (6), wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl; and pharmaceutically acceptable salts thereof. This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion, and which are accordingly useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and related diseases. The invention further relates to compositions comprising the compounds and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with the compounds.

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BIPHENYL-2-CARBOXYLIC ACID-TETRAHYDRO-ISOQUINOLIN-6-YL AMIDE DERIVATIVES,
THEIR PREPARATION AND THEIR USE AS INHIBITORS OF MICROSOMAL TRIGLYCERIDE
TRANSFER PROTEIN AND/OR APOLIPOPROTEIN B (ApoB) SECRETION

Field Of The Invention

5 This invention relates to compounds which are inhibitors of microsomal
triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion, and which are
accordingly useful for the prevention and treatment of atherosclerosis and its clinical
sequelae, for lowering serum lipids, and related diseases. The invention further relates
to compositions comprising the compounds and to methods of treating atherosclerosis,
obesity, and related diseases and/or conditions with the compounds.

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Background Of The Invention

Microsomal triglyceride transfer protein (MTP) catalyzes the transport of
triglyceride, cholesteryl ester, and phospholipids. It has been implicated as a probable
agent in the assembly of Apo B-containing lipoproteins, biomolecules which contribute
15 to the formation of atherosclerotic lesions. See European Patent application publication
no. 0 643 057 A1, European Patent application publication no. 0 584 446 A2, and
Wetterau et al., Science, 258, 999-1001, (1992). Compounds which inhibit MTP and/or
otherwise inhibit Apo B secretion are accordingly useful in the treatment of
atherosclerosis. Such compounds are also useful in the treatment of other diseases
20 or conditions in which, by inhibiting MTP and/or Apo B secretion, serum cholesterol and
triglyceride levels can be reduced. Such conditions include hypercholesterolemia,
hypertriglyceridemia, pancreatitis, and obesity; and hypercholesterolemia,
hypertriglyceridemia, and hyperlipidemia associated with pancreatitis, obesity, and
diabetes.

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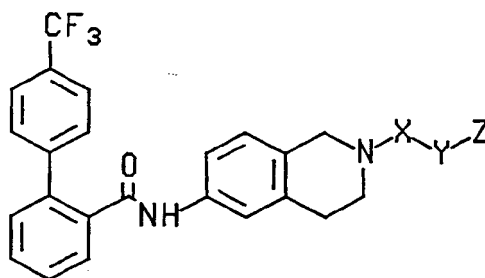
Summary Of The Invention

This invention provides compounds of formula I

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wherein

X is CH₂, CO, CS, or SO₂;

10 Y is selected from:

a direct link (i.e., a covalent bond),

aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be mono-substituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl,

15 NH, and O,

provided that if X is CH₂, Y is a direct link;

Z is selected from the following groups:

(1) H, halo, cyano,

(2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, 20 thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,

(3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH,

(4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,

25 (5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,

(6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms 30 independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic,

provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

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wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo (O=), thioxo(S=), aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl;

and pharmaceutically acceptable salts thereof.

10 Reference to Z as "heterocyclyl" means any single ring or fused ring system containing at least one ring heteroatom independently selected from O, N, and S. Thus a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated, or aromatic rings (usually benz rings) is within the definition of heterocyclyl so long as the system also contains at least one fused ring which contains
15 at least one of the aforementioned heteroatoms. As a substituent, such heterocyclyls may be attached to the remainder of the molecule from either a carbocyclic (e.g., benz) ring or from a heterocyclic ring.

Reference to Z containing "one or more rings" is intended to mean any (single or fused) cyclic moiety or moieties contained in Z. The rings may be carbocyclic or
20 heterocyclic, saturated or partially unsaturated, and aromatic or non-aromatic.

Reference to a fused polycyclic ring system or radical means that all rings in the system are fused.

Reference to "halo" in this specification is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

25 Reference to an "aryl" substituent (e.g. (C₆-C₁₀)aryl) means the ring or substituent is carbocyclic. Aromatic moieties which contain 1 or more heteroatoms are included as a subset of the term "heterocyclyl", as discussed above.

Reference to an "acyl" substituent refers to an aliphatic or cyclic hydrocarbon moiety attached to a carbonyl group through which the substituent bonds.

30 Reference to "alkyl" and "alkoxy" include both straight and branched chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

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The central benz-heterocyclic ring system of formula I, i.e., the fused bicyclic ring system attached through its single ring nitrogen to -XYZ, is referred to herein as a "1,2,3,4-tetrahydroisoquinoline" for convenience, and this is the convention used most frequently when naming compounds according to the invention as 2-substituted 1,2,3,4-tetrahydroisoquinolin-6-yl amides. It is noted that less frequently, when named as a substituent in a compound, this central ring system is also denoted as a 6-substituted "3,4,-dihydro-1H-isoquinolin-2-yl" moiety.

A subgroup of compounds of formula I as defined above includes those wherein:

- 10 X is CH₂, CO, or SO₂;
Y is selected from:
a direct link, NH,
(C₁-C₁₀)alkylene and (C₂-C₁₀)alkenylene, either of which may be substituted with phenyl,
- 15 provided that if X is CH₂, Y is a direct link,
Z is selected from the following groups:
(1) H,
(2) (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio,
(3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino,
- 20 provided that Y is not NH,
(4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl,
(5) (C₆-C₁₀)aryloxy,
(6) heterocyclyl selected from the group consisting of five- and six-membered heterocyclic radicals, which may be saturated, partially unsaturated, or aromatic, and the fused benz derivatives thereof, wherein said radicals may contain a total of from 1 to 3 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur,
- 25 provided that if X is CH₂, Z is selected from groups (4) and (6)
wherein, when Z contains one or more rings, said rings may each independently bear 0 to 3 substituents independently selected from halo, hydroxy, nitro, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, and (C₁-C₁₀)acyloxy,
- 30 and pharmaceutically acceptable salts thereof.

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A more particular subgroup includes those compounds within the above subgroup wherein X is methylene, Y is a direct link, and Z is selected from (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, and (C₄-C₈)cycloalkenyl each of which may bear 0 to 3 of the independent substituents noted for Z in the above subgroup, unsubstituted vinyl, and
5 pharmaceutically acceptable salts thereof. Specific values for each include the illustrative values for each given hereinafter.

Another more particular subgroup includes those compounds within the above subgroup wherein X is methylene or CO, Y is a direct link, and Z is heterocyclyl selected from thiophenyl, pyrrolidinyl, pyrrolyl, furanyl, thiazolyl, isoxazolyl, imidazolyl,
10 1,2,4-triazolyl, pyridyl, pyrimidinyl, and the fused bicyclic (ortho) benz derivatives thereof, including benzimidazolyl, benzthiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, quinolinyl, isoquinolinyl, and quinazolinyl, each of which may bear 0 to 3 of the independent substituents noted for Z in the above subgroup, and pharmaceutically acceptable salts thereof.

Specific values for Z as heterocyclyl which may bear 0-3 independent substituents noted for Z in the above subgroup include 2-, and 3-thiophenyl; 2- and 3-benzo[b]thiophenyl; 1-, 2- and 4-imidazolyl; 2-benzimidazolyl; 2-, 4-, and 5-thiazolyl; 2-benzothiazolyl; 3-, 4-, and 5-isoxazolyl; 2-quinoxaliny; 1-, 2-, and 3-pyrrolidinyl;
5 2-, 3-, and 4-pyridyl; 2- and 4-pyrimidinyl; 2-, 3-, and 4-quinolinyl; 1-, 3-, and 4-isoquinoline; 1-, 2-, and 3-indolyl; 1-, 2-, and 3-isoindolyl; 2- and 3-tetrahydrofuranyl; 1-, 2-, and 3-pyrrolyl; 2- and 3-furanyl; 2- and 3-benzo[b]furanyl; 1-, 3-, and 4-pyrazolyl; and 1,2,4-triazol-3-yl.

A preferred group of compounds includes those compounds wherein
10 X is CH₂ or CO;
Y is a direct link;
Z is
H, unsubstituted vinyl, phenyl,
imidazolyl, thiazolyl, thiophenyl, 1,2,4-triazolyl, pyridinyl, and pyrimidinyl
15 each of which may bear 0 to 3 of the independent substituents previously noted for the above subgroup;
and pharmaceutically acceptable salts thereof. Specific values of Z (as heterocyclyl) for this preferred group include the corresponding specific values noted above.

Within the above preferred group, a subgroup includes those compounds wherein X is CO.

Within the above preferred group, a second subgroup includes those compounds wherein X is CH₂.

- 5 The invention further provides a pharmaceutical composition suitable for the treatment of conditions including atherosclerosis, pancreatitis, obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising a compound of formula I as hereinbefore defined, and a pharmaceutically acceptable carrier.
- 10 The compounds of this invention inhibit or decrease apo B secretion, likely by the inhibition of MTP, although it may be possible that other mechanisms are involved as well. The compounds are useful in any of the diseases or conditions in which apo B, serum cholesterol, and/or triglyceride levels are elevated. Accordingly, the invention further provides a method of treating a condition selected from atherosclerosis,
- 15 pancreatitis, obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising administering to a mammal, especially a human, in need of such treatment an amount of a compound of formula I as defined above sufficient to decrease the secretion of apolipoprotein B. A subgroup of the preceding conditions includes atherosclerosis, obesity, pancreatitis, and diabetes. A more particular
- 20 subgroup includes atherosclerosis.

The term "treating" as used herein includes preventative as well as disease remitative treatment.

- The invention further provides a method of decreasing apo B secretion in a mammal, especially a human, comprising administering to said mammal an apo B-
- 25 (secretion) decreasing amount of a compound of formula I as defined above.

Certain intermediates are additionally provided as a further feature of the invention:

- 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,
- 30 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide,
- 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol,
- 6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester,

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6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, and
2-(5-amino-2-hydroxymethyl-phenyl)-ethanol.

It will be appreciated by those skilled in the art that certain compounds of formula I contain an asymmetrically substituted carbon atom and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of atherosclerosis, obesity, and the other conditions noted herein, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the treatment of the conditions noted herein by the standard tests described hereinafter.

The chemist of ordinary skill will recognize that certain combinations of substituents or moieties listed in this invention define compounds which will be less stable under physiological conditions (e.g., those containing aminal or acetal linkages). Accordingly, such compounds are less preferred.

An "aliphatic hydrocarbylene radical" for purposes of this invention means a divalent open-chain organic radical containing carbon and hydrogen only. The radical serves as a linking group, denoted above as Y. The radical may be straight chain or branched and/or saturated or unsaturated, containing up to three unsaturated bonds, either double, triple or a mixture of double and triple. The two valences may be on different carbon atoms or on the same carbon atom, and thus the term "alkylidene" is subsumed under this definition. The radical will typically be classified as a (C₁-C₂₀)alkylene radical, a (C₂-C₂₀)alkenylene radical, or a (C₂-C₂₀)alkynylene radical. Typically the radical will contain 1-10 carbon atoms, although longer chains are certainly feasible and within the scope of this invention, as demonstrated in the Examples.

Alkylene radicals include those saturated hydrocarbon groups having 1-20, preferably 1-10 carbon atoms, derived by removing two hydrogen atoms from a corresponding saturated acyclic hydrocarbon. Illustrative values having 1-10 carbon atoms include straight chain radicals having the formula (CH₂)_n wherein n is 1 to 10, such as methylene, dimethylene, trimethylene, tetramethylene, pentamethylene,

hexamethylene, heptamethylene, octamethylene, nonamethylene and so forth. Also included are alkylidene radicals such as ethylidene, propylidene, butylidene, and sec-butylidene. Also included are branched isomers such as 1,1-dimethyldimethylene, 1,1-dimethyltetramethylene, 2,2-dimethyltrimethylene and 3,3-dimethylpentamethylene.

- 5 Alkenylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one double bond. Illustrative values for alkenylene radicals having one double bond include ethenylene (vinylene), propenylene, 1-butenylene, 2-butenylene, and isobutenylene.
- 10 Alkenylene radicals containing two double bonds (sometimes referred to in the art as alkadienylene radicals) include 3-methyl-2,6-heptadienylene, 2-methyl-2,4-heptadienylene, 2,8-nonadienylene, 3-methyl-2,6-octadienylene, and 2,6-decadienylene. An illustrative value for an alkylene radical containing three double bonds (an alkatrienylene radical) is 9,11,13-heptadecatrienylene.
- 15 Alkynylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one triple bond. Illustrative values include ethynylene, propynylene, 1-butynylene, 1-pentynylene, 1-hexynylene, 2-butynylene, 2-pentynylene, 3,3-dimethyl-1-butynylene, and so forth.
- 20 Following are illustrative values for other moieties and substituents named above, which are not to be taken as limiting. It is noted that throughout the specification, if a cyclic or polycyclic radical which can be bonded through different ring atoms is referred to without noting a specific point of attachment, all possible points are intended, whether through a carbon atom or a trivalent nitrogen. As examples,
- 25 reference to (unsubstituted) "naphthyl" means naphth-1-yl and naphth-2-yl; reference to "pyridyl" means 2-, 3-, or 4-pyridyl; reference to "indolyl" means attachment or bonding through any of the 1-, 2-, 3-, 4-, 5-, 6-, or 7- positions.
- Illustrative values for (C₁-C₁₀)alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy, and so forth.
- 30 Illustrative values for (C₁-C₁₀)alkylthio include the corresponding sulfur-containing compounds of (C₁-C₁₀)alkoxy listed above, including methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, heptylthio, and so forth.

Illustrative values for (C₁-C₁₀)acyl include values for (C₁-C₁₀)alkanoyl such as formyl, acetyl, propionyl, butyryl, and isobutyryl. Also included are other common cycle-containing radicals such as benzoyl.

Illustrative values for (C₁-C₁₀)acyloxy include values for (C₁-C₁₀)alkanoyloxy such as formyloxy, acetyloxy, propionyloxy, butyryloxy, and isobutyryloxy. Also included are other common cycle-containing radicals such as benzoyloxy.

Illustrative values for (C₁-C₁₀)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, and isobutoxycarbonyl.

Illustrative values for (C₁-C₁₀)alkylamino include methylamino, ethylamino, propylamino, isopropylamino, butylamino, and isobutylamino.

Illustrative values for di-(C₁-C₁₀)alkylamino include dimethylamino, diethylamino, dipropylamino, dibutylamino, and diisobutylamino.

Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino are benzylamino, (1-phenylethyl)amino, and (2-phenylethyl)amino.

Illustrative values for (C₆-C₁₀)aryl include phenyl and naphthyl.

Illustrative values of (C₃-C₈)cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

Illustrative values for fused benz derivatives of (C₃-C₈)cycloalkyl include 1,2,3,4-tetrahydronaphthalenyl, indanyl, and fluorenyl.

Illustrative values of polycycloalkyl include adamantyl and 2-bicyclo[2.2.1]heptyl.

Illustrative values for (C₄-C₈)cycloalkenyl include cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

Illustrative values for polycycloalkenyl include bicyclo[3.1.1]hept-2-enyl.

Illustrative values for (C₆-C₁₀)aryloxy include phenoxy and naphthyloxy.

Illustrative values for (C₆-C₁₀)arylthio include phenylthio and naphthylthio.

Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy include benzyloxy and phenylethoxy.

Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio include benzylthio and phenylethylthio.

Illustrative values for (C₃-C₈)cycloalkyloxy include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and cycloheptyloxy.

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Illustrative values for (C₄-C₈)cycloalkenyloxy include cyclobutenyloxy, cyclopentenylloxy, cyclohexenyloxy, and cycloheptenyloxy.

Illustrative values for heterocyclyl substituents which are five-member monocyclic radicals include furanyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, and 1,3,4-thiadiazolyl, and the like.

Illustrative values for heterocyclyl substituents which are six-membered monocyclic radicals include 2H- and 4H-pyranyl, pyridyl, piperidinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, morpholinyl, thiomorpholinyl, 1,3,5-triazinyl, and the like.

Illustrative values for heterocyclyl substituents which are fused benz derivatives of five-membered heterocyclic radicals include indolyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzthiazolyl, and carbazolyl.

Illustrative values for heterocyclyl substituents which are fused benz derivatives of six-membered heterocyclic radicals include quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, phenothiazinyl, acridinyl, and phenoxazinyl.

Illustrative examples for heterocyclyl groups which are fused polycyclic radicals other than the fused benz systems exemplified above include purinyl and pteridinyl.

Illustrative values of (C₁-C₁₀)alkyl include methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, pentyl, hexyl, and the like.

Illustrative values for (C₁-C₃)perfluoroalkyl include trifluoromethyl, pentafluoroethyl, and heptafluoropropyl.

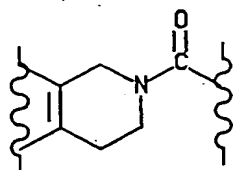
Illustrative values for (C₁-C₃)perfluoroalkoxy include trifluoromethoxy and pentafluoroethoxy.

Compounds according to the invention can frequently be categorized into groups based on the linking group formed by the ring nitrogen of the 1,2,3,4-tetrahydroisoquinoline ring (shown in formula I) taken together with the group in -XYZ which links the XYZ moiety to the said ring nitrogen. Such categories include

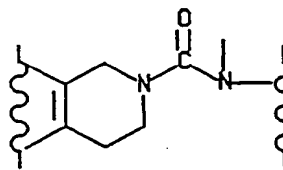
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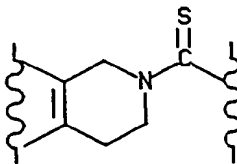


Amides

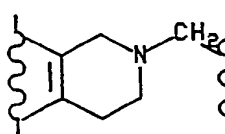


Ureas

10

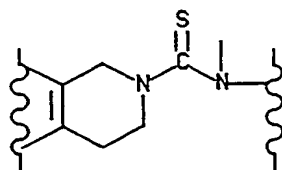


Thioamides

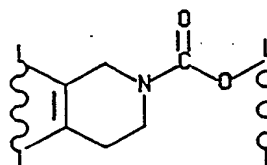


N-alkyls

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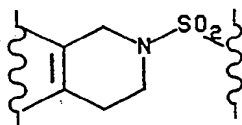


Thioureas



Carbamate

20



Sulfonamides

25

Referring to the above linking groups as illustrated, for amides and thioamides
 30 (X=CO or CS, respectively) Y is preferably a direct link or hydrocarbylene. In these compounds wherein Y is a direct link, bonding is preferably through the carbonyl or thiocarbonyl group to an aliphatic (i.e., open chain) carbon atom in Z. The said aliphatic carbon atom can be part of a chain which contains one or more heteroatoms.

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Bonding can also preferably be through the carbonyl or thiocarbonyl group to a cyclic carbon atom. By "cyclic carbon atom" is meant a saturated or unsaturated carbon atom contained in a (saturated, partially unsaturated, or aromatic) carbocyclic or heterocyclic ring. For compounds wherein Y is hydrocarbylene, bonding is through the
5 carbonyl or thiocarbonyl group to an aliphatic carbon atom in Y.

For ureas and thioureas wherein $X=CO$ or CS , respectively and $Y=NH$, bonding is preferably through the (easternmost as shown) amino group to a cyclic carbon atom in Z. For some ureas and thioureas ($X=CO$, $Y=direct\ bond$) the (easternmost) amino nitrogen is part of Z. In this case bonding is preferably through the easternmost amino
10 group to an aliphatic carbon atom in the remaining portion of Z.

For sulfonamides according to the invention $X=SO_2$ and Y is preferably hydrocarbylene, or a direct link. For sulfonamides wherein Y is hydrocarbylene, bonding is through the sulfonyl group to an aliphatic carbon atom in Y. For sulfonamides wherein Y is a direct link, bonding is preferably through the sulfonyl group
15 to a cyclic carbon atom in Z. For sulfonamides wherein Y is a direct link, bonding can also be to NH which is part of Z, in which case bonding is through X directly to an amino nitrogen in Z.

N-alkyls ($X=CH_2$, $Y=direct\ link$) preferably bond through the methylene group to a cyclic carbon atom in Z.

20 For carbamates wherein $X=CO$ and $Y=O$ bonding is preferably through the oxy (O) portion of the linkage to a cyclic carbon atom in the remaining portion of Z. For carbamates wherein $X=CO$ and $Y=direct\ link$ the oxy linkage is part of Z, and in these bonding is preferably to a cyclic or aliphatic carbon atom in the remaining portion of Z, most preferably to an aliphatic carbon atom in the remaining portion of Z.

25 For those compounds of formula I wherein Y is hydrocarbylene, bonding to Z is through an aliphatic carbon atom in Y preferably to H or to a cyclic carbon atom or a heteroatom in Z.

When grouping compounds below and in the Examples, it is the above structural categories to which reference is made.

30 Preferred compounds include the following which, where possible, have been categorized according to the types of linking groups shown in partial structure above.

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AMIDES

- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenyl-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide
- 5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pentanoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide
- 10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclobutane-carbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetra-
- 15 hydroisoquinolin-6-yl]-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-butyryl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide
- 20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-fluoro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide
- 25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-but-3-enoyl-1,2,3,4-tetrahydro-
- 30 isoquinolin-6-yl)-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-methoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

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- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethylthio-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide
- 5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-diethyl-carbamoyl-cyclohex-3-enecarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(cyclopent-1-enyl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide
- 10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-hex-3-enoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide
- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(tetrahydrofuran-3-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide
- 15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-3-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide
- 20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(pyridine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

UREAS

- 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenylamide
- 25 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid hexylamide
- 30 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-di-hydro-1H-isoquinoline-2-carboxylic acid benzylamide

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6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid [(R)-1-phenyl-ethyl]-amide

5 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid pyridin-2-ylamide

SULFONAMIDES

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(propane-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-dimethylsulfamoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-trifluoromethoxy-benzenesulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

THIOUREAS

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclopropylthiocarbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

N-ALKYLS

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,6,6-trimethyl-cyclohex-2-enylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,4-dichloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1,5a,6,9,9a,9b-hexahydro-4H-dibenzofuran-4a-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-pyrrol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-furan-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Acetic acid 5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-furan-2-ylmethyl ester

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-3-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,5-dimethoxy-tetrahydrofuran-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-quinolin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyrimidin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

30

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-nitro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-pyrrol-2-ylmethyl)-1,2,3,4-
5 tetrahydroisoquinolin-6-yl]-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-benzoimidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

4'-trifluoromethyl-biphenyl-2-carboxylic acid [(2-allyl)-1,2,3,4-tetrahydro-
20 isoquinoline-6-yl] amide

CARBAMATES

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

25

Particularly preferred compounds include the following:

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

30

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid (1-phenyl-ethyl)-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

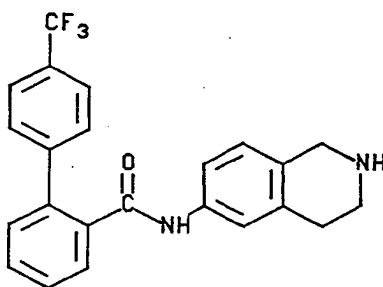
4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide, and

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

Detailed Description

In the discussion which follows, common chemical abbreviations and acronyms have been employed: Me (methyl); Et (ethyl); THF (tetrahydrofuran); BOC (tert-butyloxycarbonyl, a blocking group); Ms (methanesulfonyl, mesyl); TFA (trifluoroacetic acid); Ac (Acetyl); RP (reverse phase); HPLC (high performance liquid chromatography);

Compounds of formula I can be made by processes which include processes known in the chemical arts for the production of similar compounds. Such processes for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which the meanings of generic radicals are as given above unless otherwise qualified. The processes involve treating a compound of formula II,



II

which contributes the western portion of the molecule (i.e., the moiety consisting of formula II with the hydrogen removed from the tetrahydroisoquinoliny ring nitrogen) with a reactant which adds the eastern (XYZ) moiety. Reactants which furnish the eastern moiety are generally commercially available or well preceded in the scientific literature. The compound of formula II is 4'-trifluoromethylbiphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)amide and is referred to herein simply as "compound II" for the sake of convenience. The western portion of the molecule it contributes to compounds according to the invention is the 6-[(4'-trifluoromethyl)biphen-2-ylcarbonylamino]-3,4-dihydro-1H-isoquinolin-2-yl moiety.

10 The processes can be effected, generally:

(a) for a compound of formula I wherein X is carbonyl, by treating compound II with a carboxylic acid of formula Z-Y-COOH in the presence of a coupling reagent. The coupling reagent is typically a carbodiimide, preferably 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide which is known by the acronym EDC and can be obtained commercially. The EDC can advantageously be polymer bound as disclosed in U.S. patent 5,416,193. The reaction is typically conducted at room temperature and in an inert solvent, although heating can be employed if desired. Typical reaction spans vary anywhere from a few minutes to 48 hours, typically overnight.

(b) for a compound of formula I wherein X is carbonyl or thiocarbonyl, by treating compound II with an activated form of a corresponding carboxylic acid or thiocarboxylic acid, in the presence of a base. Typically the activated form is the corresponding acid chloride of formula Z-Y-COCl or Z-Y-CSCl, respectively. The base is, for example, an amine which may advantageously be bound to a polymer to reduce cleanup, a typical bound base being polymer bound morpholinomethyl-polystyrene. The reaction is generally conducted at room temperature with stirring, shaking or other form of agitation for a time necessary to allow the reaction to proceed to a reasonable degree if not to completion, typically 2-48 hours, typically overnight.

Compounds made as disclosed in (a) and (b) above form structural types previously referred to as amides and thioamides.

30 (c) for a compound of formula I wherein X is carbonyl or thiocarbonyl and Y is NH, by treating compound II with, respectively, a corresponding isocyanate of formula Z-N=C=O or thioisocyanate of formula Z-N=C=S, respectively. The resulting products are compounds according to the invention referred to herein by structural type as ureas

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and thioureas, respectively. The reaction is generally conducted in an inert solvent, typically a halogenated hydrocarbon such as 1,2-dichloroethane, typically for a time of 2-48 hours, usually overnight.

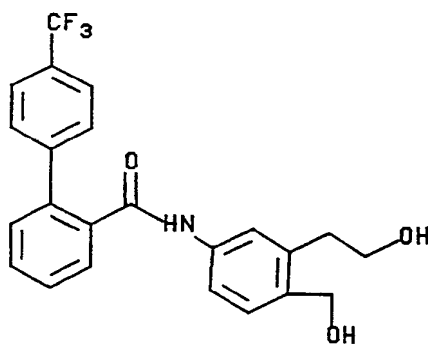
(d) for a compound of formula I wherein X is sulfonyl, by treating compound II
5 with a corresponding sulfonyl chloride of formula Z-Y-SO₂Cl. The resulting product is of the sulfonamide structural type. The reaction is typically conducted in an inert solvent such as a halogenated hydrocarbon (e.g., 1,2-dichloroethane), at room temperature for several hours or more, typically overnight.

(e) for a compound of formula I wherein X is CH₂ and Y is a direct link, by
10 treating compound II with an aldehyde of formula Z-CHO in the presence of sodium triacetoxyborohydride. This is essentially the reductive amination reported in Abdel-Magid et al., Tetrahedron Lett., 31(39), 5595-5598 (1990). The resulting product is of the N-alkyl structural type. The reaction is conducted in an appropriate solvent such as a halogenated hydrocarbon, with shaking or agitating otherwise for a time of from
15 a few hours to several days at room temperature, although heat can be applied to increase reaction rate if desired.

(f) for a compound of formula I wherein X is CH₂ and Y is a direct link, by treating a compound of the formula

20

25



III

with a corresponding compound of the formula Z-CH₂-NH₂, in the presence of mesyl
30 chloride, typically two equivalents.

(g) for a compound of formula I wherein X is thiocarbonyl by treating a corresponding compound of formula I wherein X is CO with phosphorus pentasulfide, P₄S₁₀. The reaction can be carried out conventionally by using a stoichiometric amount

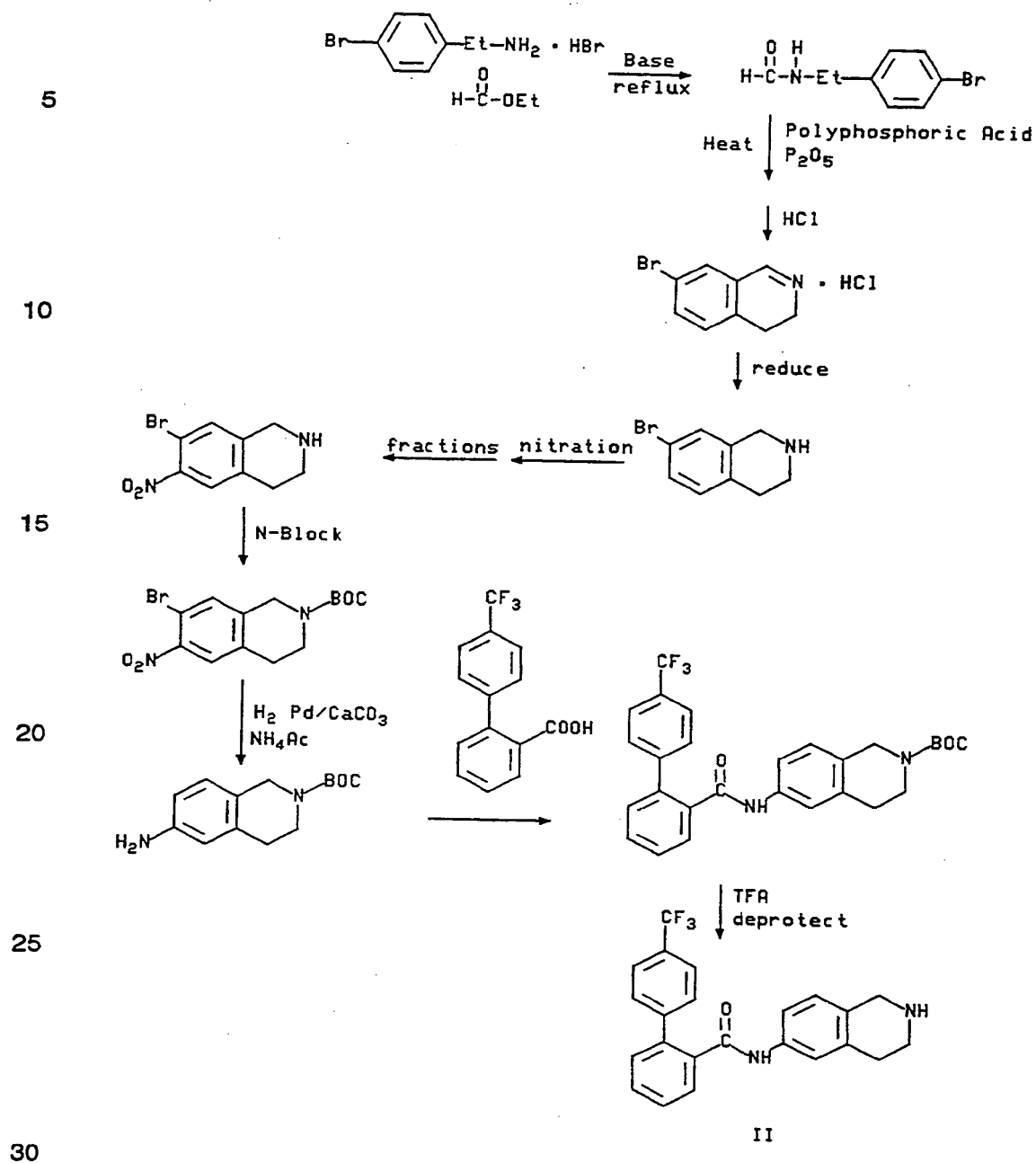
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of P_4S_{10} (or an excess if desired) and heating it together with the corresponding amide in an inert solvent such as pyridine, xylene, benzene, chlorobenzene or toluene. The reaction is usually implemented at reflux for anywhere from a few minutes to a few hours.

- 5 The compound of formula II can be made as outlined in Scheme I and as specifically exemplified in Example 1. Referring to Scheme I, 2-(4-bromophenyl)ethylamine hydrobromide is reacted with ethyl formate in the presence of a base to make N-[2-(4-bromophenyl)ethyl]formamide. The formamide is then treated with phosphorus pentoxide in polyphosphoric acid to cyclize, followed by
- 10 treatment with hydrogen halide (e.g., HCl) gas to form the hydrohalide salt of 7-bromo-3,4-dihydroisoquinoline hydrohalide. The hydrohalide salt is then reduced to afford 7-bromo-1,2,3,4-tetrahydroisoquinoline. The reduced material is then nitrated by treatment with potassium nitrate in concentrated sulfuric acid and the appropriate fraction separated to yield 7-bromo-6-nitro-1,2,3,4-tetrahydroisoquinoline. The nitrated
- 15 material is then reacted with di-tert-butyl dicarbonate in the presence of a base to block the ring tetrahydroisoquinoline nitrogen, thereby affording 7-bromo-6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester. The ester is then hydrogenated in the presence of palladium-on-calcium carbonate to form the corresponding 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ester. The amine is then reacted with 4'-
- 20 trifluoromethylbiphenyl-2-carboxylic acid to form 6-[4'-trifluoromethylbiphenyl-2-carbonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester. This product can then be deblocked conventionally to make compound II, 4'-trifluoromethylbiphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)amide.

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SCHEME I

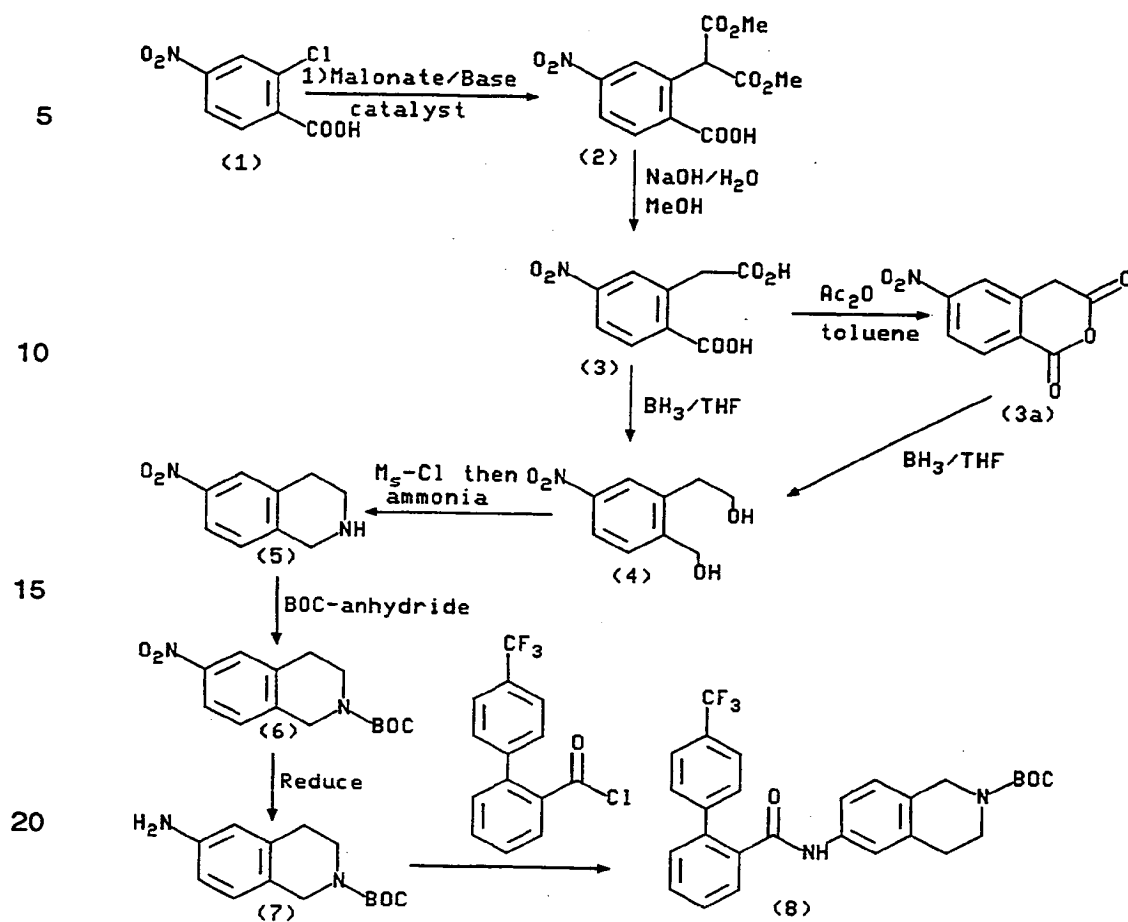


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The compound of formula II can, alternatively, be made by a second route as illustrated in Scheme 2. Referring to Scheme 2, nitrobenzoic acid (1) can be treated with dimethyl malonate in the presence of base to form compound (2). Compound (2) can then be treated with aqueous alcoholic base to effect hydrolysis and decarboxylation to yield compound (3). Compound (3) can, if desired, be treated with acetic anhydride in toluene or other hydrocarbon solvent to make anhydride (3a). Reduction of compound (3) or (3a) affords the corresponding diol (4) which can then be treated with mesyl chloride to form the dimesylate which is subsequently cyclized with ammonia, thereby affording compound (5). Compound (5) is then conventionally N-blocked to yield compound (6), which in turn is reduced to make corresponding amine (7). Amine (7) can then be treated with the acid chloride of 4'-trifluoromethylbiphenyl-2-carboxylic acid (made by treating the corresponding free acid with thionyl chloride) to make the corresponding amide analog (8) of compound II. Compound (8) can be deblocked conventionally, as illustrated and discussed in Scheme I, to afford compound II.

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SCHEME 2



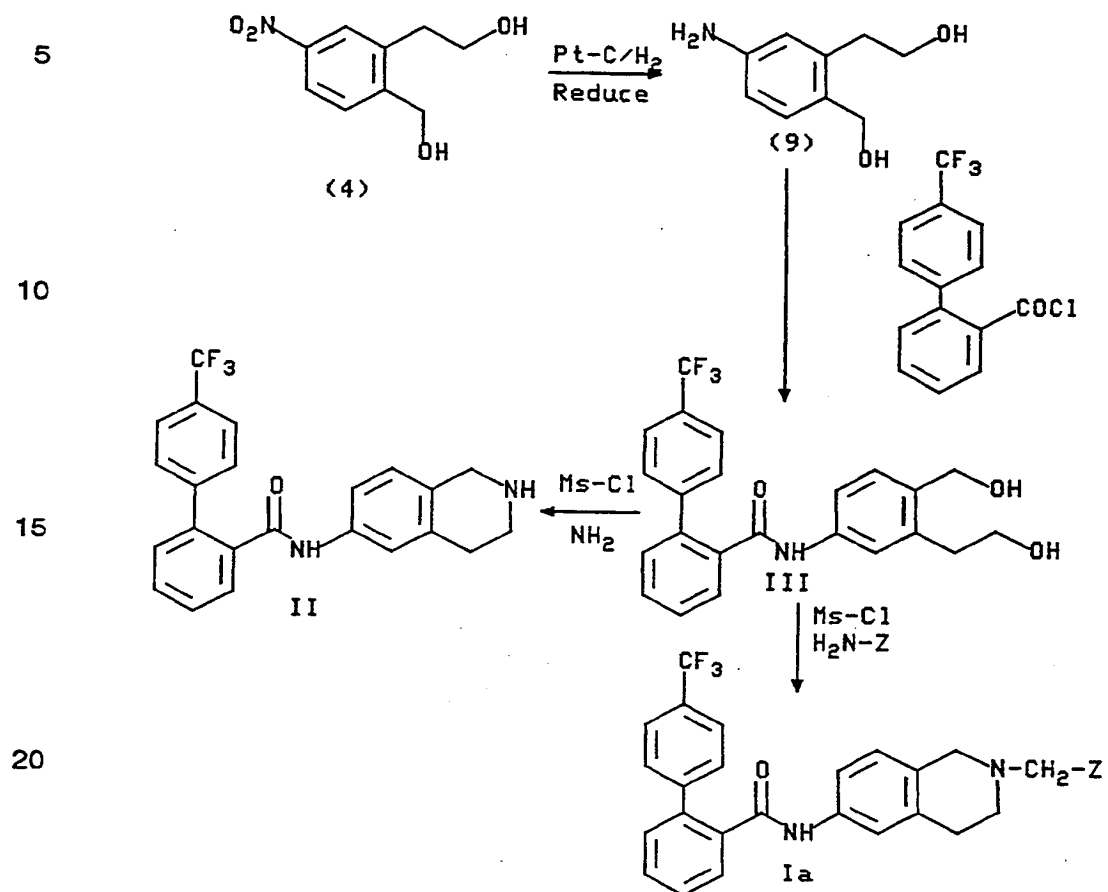
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The compound of formula III can be made as illustrated in Scheme 3 starting with the diol (4) first shown in Scheme 2. Referring to Scheme (3), diol (4) is reduced with hydrogen in the presence of platinum-on-carbon catalyst to make corresponding amino diol (9). Amino diol (9) can then be reacted with the acid chloride of 4'-trifluoromethylbiphenyl-2-carboxylic acid to afford compound III. Compound III can, as shown, then be cyclized with ammonia in the presence of a catalyst to make compound II.

As also shown in Scheme 3, compound III can also be reacted directly with a corresponding amine of formula $Z-CH_2-NH_2$ in the presence of base and catalyst to make a compound of formula I, designated Ia in Scheme 3, wherein X is CH_2 and Y is a direct link.

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SCHEME 3



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Conventional methods and/or techniques of purification and separation known to those skilled in the art can be used to isolate the compounds of this invention. Such techniques include all types of chromatography (HPLC, column chromatography using common adsorbents such as silica gel, and thin layer chromatography),
5 recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compounds herein form cationic salts such as acid addition salts and the expression "pharmaceutically-acceptable salts" is intended to define but not be limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate,
10 methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. For many compounds polyaddition salts are feasible.

The acid addition salts of the compounds of the present invention are readily prepared by reacting the base forms with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the
15 acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid
20 will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The compounds of the present invention are orally administrable and are accordingly used in combination with a pharmaceutically acceptable carrier or diluent
25 suitable to oral dosage forms. Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described below. Thus, for oral administration the compounds can be combined with a suitable solid or liquid carrier
30 or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin.

- 5 When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a
10 sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

These active compounds may also be administered parenterally. For parenteral administration the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Solutions or suspensions of these active
15 compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in sesame or peanut oil, ethanol, water, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, vegetable oils, N-methyl glucamine, polyvinylpyrrolidone and mixtures thereof in oils as well as aqueous solutions of water-soluble pharmaceutically
20 acceptable salts of the compounds. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly.

The pharmaceutical forms suitable for injectable use include sterile aqueous
25 solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

30 The dose of a compound of formula I which is administered will generally be varied according to principles well known in the art taking into account the severity of the condition being treated and the route of administration. In general, a compound of formula I will be administered to a warm blooded animal (such as a human) so that

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an effective dose, usually a daily dose administered in unitary or divided portions, is received, for example a dose in the range of about 0.1 to about 15 mg/kg body weight, preferably about 1 to about 5 mg/kg body weight. The total daily dose received will generally be between 1 and 1000 mg, preferably between 5 and 350 mg.

5 The compounds of this invention may be used in conjunction with other pharmaceutical agents, including other lipid lowering agents. Such agents include cholesterol biosynthesis inhibitors, especially HMG CoA reductase inhibitors and squalene synthetase inhibitors; bile acid sequestrants; fibrates; cholesterol absorption inhibitors; and niacin.

10 A test compound is considered to be active if it is active in any of the following screens.

The activity of a compound according to the invention can be assessed by measuring inhibition of apo B secretion in HepG2 cells.

HepG2 cells are grown in Dulbecco's Modified Eagles Medium plus 10% fetal
15 bovine serum (growth medium; Gibco) in 96-well culture plates in a humidified atmosphere containing 5% carbon dioxide until they are approximately 70% confluent. Test compounds are dissolved at 10-20 mM in dimethyl sulfoxide which is then diluted to 1 μ M in growth medium. Serial 1:1 dilutions of this stock are made in growth medium and 100 μ l of each are added to separate wells of a 96-well culture plates
20 containing HepG2 cells. Twenty four hours later, growth medium is collected and assayed by specific ELISA for apoB and, as a control, apoAI concentrations. Inhibitors are identified as compounds that decrease apoB secretion into the medium without affecting the secretion of apoAI. The ELISA for apoB is performed as follows. Monoclonal antibody against human apoB (Chemicon) is diluted to 5 μ g/ml in
25 phosphate buffered saline/azide (PBS + 0.02% Na azide) and 100 μ l are added to each well of a 96-well plate (NUNC Maxisorb). After an overnight incubation at room temperature, the antibody solution is removed and wells are washed 3 times with PBS/azide. Non-specific sites on the plastic are blocked by incubating wells for 1-3 hours in a solution of 1% (w/v) bovine serum albumin (BSA) made in PBS/azide. 100
30 μ l of various dilutions of growth medium from the HepG2 cells or apoB standards (made in 0.004% Tween 20/1% BSA in PBS/azide) are added to each well and incubated for 18 hours. Wells are aspirated and washed 3 times (0.1% Tween 20 in PBS) prior to adding 100 μ l of a 1/1000 dilution of the secondary antibody, goat anti-

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human apoB (Chemicon). After a 3 hr incubation at room temperature, this solution is aspirated and the wells are again washed 3 times as above. 100 μ l of a 1:1600 dilution (in PBS/1% BSA/2mM $MgCl_2$) of rabbit anti-goat IgG conjugated to alkaline phosphatase (Sigma) are then added to each well and incubated for 1 hr at room temperature. After aspirating, the wells are washed 4 times as above and 100 μ l of 1 mg/ml p-nitrophenylphosphate (pNPP; Sigma) in 25 mM sodium (bi)carbonate/2 mM $MgCl_2$, pH 9.5, are added to each well and incubated for 20-30 minutes and then the reaction is terminated by the addition of 50 μ l of 0.2N NaOH. Absorbance of each well is read at 405 nm and the background at 650 nm is subtracted. ApoB concentration is calculated from a standard curve constructed from purified LDL standards that are run in parallel in the same assay. ApoA1 is measured in an analogous manner except that antibodies for apoA1 (Chemicon) are used in place of the antibodies for apoB and antigen incubation is at 37° instead of room temperature.

Activity can also be confirmed if a test compound inhibits MTP activity directly.

Inhibition of MTP activity by a compound can be quantitated by observing the inhibition of transfer of radiolabeled triglyceride from donor vesicles to acceptor vesicles in the presence of soluble human MTP. The procedure for preparing MTP is based on the method of Wetterau and Zilversmit (Biochem. Biophys. Acta (1986) 875:610). Briefly, human liver chunks, frozen at -80°C, are thawed on ice, minced, and rinsed several times with ice cold 0.25 M sucrose. All subsequent steps are performed on ice. A 50% homogenate in 0.25 M sucrose is prepared using a Potter-Elvehjem Teflon pestle. The homogenate is diluted 1:1 with 0.25 M sucrose and centrifuged at 10,000 x g for 20 min at 4°C. The pellet is resuspended in sucrose and recentrifuged at 10,000 x g for 20 min. The supernatants are combined and the microsomes pelleted by centrifugation at 105,000 x g for 75 min. The supernatant is discarded and the microsomal pellet is suspended in a minimal volume of 0.25 M sucrose, diluted to 3 ml per gm starting liver weight with 0.15 M Tris-HCl pH 8.0. This suspension is divided into 12 fractions, and centrifuged at 105,000 x g for 75 min. The supernatants are discarded and the microsomal pellets are stored frozen at -80°C until needed. For preparation of MTP prior to performing the assay, a thawed pellet is suspended in 12 ml of cold 50 mM Tris-HCl, 50 mM KCl, 5 mM $MgCl_2$, pH 7.4 and 1.2 ml of a 0.54% deoxycholate (pH 7.4) solution is added slowly with mixing to disrupt the microsomal membrane. After a 30 min incubation on ice with gentle mixing, the suspension is

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centrifuged at 105,000 x g for 75 min. The supernatant, containing the soluble MTP protein, is dialyzed for 2-3 days with 4 changes of assay buffer (150 mM Tris-HCl, 40 mM NaCl, 1 mM EDTA, 0.02% NaN₃, pH 7.4). The human liver MTP is stored at 4°C and diluted 1:5 with assay buffer just before use. MTP preparations show no notable
5 loss of transfer activity with storage up to 30 days.

Liposomes are prepared under nitrogen by room temperature, bath sonication of a dispersion of 400 μ M egg phosphatidylcholine (PC), 75 μ M bovine heart cardiolipin, and 0.82 μ M [14C]-triolein (110 Ci/mol) in assay buffer. The lipids in chloroform are added in the proper amounts and dried under a nitrogen stream before hydrating with
10 assay buffer. Acceptor liposomes are prepared under nitrogen by room temperature bath sonication of a dispersion of 1.2 mM PC, 2.3 μ M triolein and 30 pM [3H]-PC (50 Ci/mol) in assay buffer. The donor and acceptor liposomes are centrifuged at 160,000 x g for 2 hrs at 7°C. The top 80% of the supernatant, containing small unilamellar liposomes, are carefully removed and stored at 4°C until used for transfer assays.

15 MTP activity is measured using a transfer assay which is initiated by mixing donor and acceptor vesicles together with the soluble MTP and test compound. To 100 μ l of either a 5% BSA (control) or 5% BSA containing the test compound, are added 500 μ l assay buffer, 100 μ l donor liposomes, 200 μ l acceptor liposomes and 100 μ l of diluted MTP protein. After incubation at 37°C for 45 min., triglyceride transfer is
20 terminated by adding 500 μ l of a 50% (w/v) DEAE cellulose suspension in assay buffer. Following 4 min of agitation, the donor liposomes, bound to the DEAE cellulose, are selectively sedimented by low speed centrifugation. An aliquot of the supernatant containing the acceptor liposomes is counted and the 3H and 14C counts are used to calculate the percent recovery of acceptor liposomes and the percent triglyceride
25 transfer using first order kinetics. Inhibition of triglyceride transfer by test compound is manifest as a decrease in 14C radioactivity compared to controls where no test compound is present.

Activity of test compounds as MTP inhibitors can also be measured *in vivo* according to the following test.

30 Male mice (20-30g.; various strains) are dosed by oral gavage (0.25 ml/25 g. body weight) with test compound suspended in an aqueous 0.5% methyl cellulose solution. Compound solutions are dosed either multiple times over several days or, alternatively, once 90 minutes before mice are euthanized and blood is collected for

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preparation of serum. The serum is assayed for triglyceride concentration by a commercial enzymatic assay (Triglyceride G: Wako Fine Chemicals). MTP inhibitors are identified by their ability to lower serum triglycerides as compared to control mice dosed with vehicle.

- 5 The present invention is illustrated by the following Examples. However, it should be understood that the invention is not limited to the specific details of these examples.

Example 1

This example illustrates how to make the intermediate compound of formula II

10 N-[2-(4-Bromo-phenyl)-ethyl]-formamide

- 500 g (1.78 mol) of 2-(4-bromo-phenyl)-ethylamine hydrobromide, 1 liter (12.4 mol) of ethyl formate and 248 ml (1.78 mol) of triethylamine were combined and heated to reflux for 3 hrs. The reaction was treated with 1 liter each of deionized water and ethyl acetate. The organic layer was separated and washed with 1 liter each of water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to yield 378 g of a solid.

MS (CI): 245 (M + NH₄⁺)

7-Bromo-3,4-dihydro-isoquinoline hydrochloride

- 20 In a 12 liter three neck round bottom flask, 4 kg of polyphosphoric acid was heated to 150°C and stirred. To the stirring polyphosphoric acid was added 530 g (3.75 mol) of phosphorus pentoxide in three portions of approximately 176.7 g each. After the phosphorus pentoxide had dissolved, 378 g (1.66 mol) of N-[2-(4-bromo-phenyl)-ethyl]-formamide was added. The reaction temperature was then raised to 200°C and maintained for two hours. At this point, the reaction temperature was allowed to cool to 160°C and poured onto 16 liters of ice. The mixture was stirred for 0.5 hours, basified to pH 12 with 10N sodium hydroxide solution and extracted three times with 3 liters of dichloromethane. The combined organic layers were washed with 1 liter of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The oil was dissolved in 2.5 liters of methanol and saturated with anhydrous HCl gas. The resulting solution was concentrated to one liter volume and 1 liter of diethyl ether was added. The resulting precipitate was filtered, washed with diethyl ether and air dried to yield 219 g of a solid.

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MS (CI): 210 (M + H⁺)7-Bromo-1,2,3,4-tetrahydroisoquinoline

219 g (0.89 mol) of 7-bromo-3,4-dihydro-isoquinoline hydrochloride and 1.5 liters
5 of water were combined and heated to 50°C. 33.7g (0.89 mol) of sodium borohydride
was added in portions over 0.5 hours at which time the temperature rose to 62°C. The
reaction was then cooled to ambient temperature and extracted three times with 1 liter
of dichloromethane. The combined organic layers were washed with 1 liter of saturated
sodium chloride solution, dried over anhydrous sodium sulfate and concentrated to
10 yield 173 g of an oil.

MS (CI): 212 (M + H⁺)7-Bromo-6-nitro-1,2,3,4-tetrahydroisoquinoline

In a 5 liter three neck round bottom flask, 173 g (0.813 mol) of 7-bromo-1,2,3,4-
15 tetrahydroisoquinoline was dissolved carefully into 950 ml of concentrated sulfuric acid.
The resulting solution was cooled to -5°C and a solution of 82.7g (0.816 mol) of
potassium nitrate in 1 liter of concentrated sulfuric acid was added dropwise. After
addition, the reaction was maintained at -5°C for 15 minutes and poured onto 3 liters
of ice. The resulting mixture was basified to pH 14 with 50% sodium hydroxide
20 solution. The basic solution was extracted three times with 1 liter of dichloromethane.
The combined organic layers were washed with 1 liter each of water and saturated
sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate,
filtered and concentrated to yield 201g of an oil. The oil preadsorbed onto silica gel
was charged onto a column of 4 kg of silica gel and eluted with a gradient of 1-5%
25 methanol/dichloromethane. The fractions containing product were combined and
concentrated to yield 115 g of a solid.

¹H NMR (300 MHz, CDCl₃) δ 7.61 (s, 1H); 7.38 (s, 1H); 4.10 (s, 2H); 3.20 (t, 2H);
2.90 (t, 2H).

7-Bromo-6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

30 215 g (0.447 mol) of 7-bromo-6-nitro-1,2,3,4-tetrahydroisoquinoline, 45.2 g (0.447
mol) of TEA, 97.5 g (0.447 mol) of di-*tert*-butyl dicarbonate, 3.2 liter of dioxane and 0.5
liter of water were combined and stirred at ambient temperature for 1.5 hrs. The
reaction was concentrated to remove the dioxane, 1 liter of saturated sodium

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bicarbonate was added and extracted two times with 1 liter of dichloromethane. The organic layer was extracted with brine, dried over magnesium sulfate and concentrated. The resulting solid was recrystallized from isopropanol to yield 118 g of a solid.

¹H NMR (250 MHz, DMSO) δ 7.89 (s, 1H); 7.81 (s, 1H); 4.58 (s, 2H); 3.56 (t, 2H);
5 2.81 (t, 2H); 1.42 (s, 9H).

6-Amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

59 g (0.16 mol) of 7-bromo-6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, 10 g of 5% palladium on calcium carbonate and 49 g of ammonium
10 acetate in 1 liter of acetic acid was hydrogenated on a Parr shaker for 5 hrs. The reaction was filtered through Celite, concentrated, basified to pH 12 with 4N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to yield 40 g of an oil.

¹H NMR (300 MHz, DMSO) δ 4.87 (s, 2H); 4.27 (s, 2H); 3.44 (t, 2H); 2.57 (t, 2H);
15 1.39 (s, 9H).

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

7.6 g (29 mmol) of 4'-trifluoromethyl-biphenyl-2-carboxylic acid, 7.1 g (29 mmol)
20 of 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, 100 mg of DMAP and 6.1 g (32 mmol) of EDCI were mixed in 130 ml of methylene chloride for 12 hrs. Reaction was extracted with 2 x 150 ml 1N HCl, 2 x 150 ml 1N NaOH, 150 ml water, brine and concentrated to yield 14 g of a beige foam.

MS (Cl): 519 (M + Na⁺)

25 ¹H NMR (250 MHz, CDCl₃) δ 4.49 (s, 2H); 3.60 (t, 2H); 2.77 (t, 2H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

4 g (8 mmol) of 6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester and 6 ml (78 mmol) of TFA were mixed in
30 60 ml of methylene chloride for 5 hrs. 40 ml of methylene chloride was added and organic was extracted with 3 x 50 ml of saturated sodium bicarbonate and brine. Organic layer was dried over sodium sulfate and concentrated to yield 3.1 gm of solid.

MS (Cl): 397 (M + H⁺)

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The following compounds, classified as amides by the criteria previously set forth, were synthesized by the procedure described in method A.

Method A

5 Into a glass screw topped vial was placed 150 μ l of a 0.020M solution of the acid chloride in 1,2-dichloroethane (3.0 μ mol), followed by 83 μ l of 0.030M 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide in 1,2-dichloroethane (2.5 μ mol), followed by 25 mg polymer bound morpholinomethylpolystyrene (@2.5 μ mol/gm=62 μ mol). After shaking at 20°C for 16
10 hours, 10 μ l was removed and diluted to 100 μ l with methanol for RPHPLC and MS analysis. The polymer was removed by filtration and the filtrate was concentrated to dryness under vacuum.

Example 2

By Method A described above, 4'-trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-
15 cyclopentyl-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide was made by reacting compound II with 3-cyclopentylpropionyl chloride in the presence of polymer-bound morpholine.

MS (CI): 521 (M + H⁺)

20

Examples 3-39

The following compounds were made according to methods analogous to those described in Example 2 by reacting compound II with the appropriate corresponding acid chloride.

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenylacetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 515 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 4.68 and 4.53 (s, 2H); 3.80 (s, 2H); 3.80 and 3.61 (t, 2H); 2.76 and 2.59 (t, 2H).

30

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 501 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide

MS (CI): 491 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-chloro-buteryl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 501 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzyloxyacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 545 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-heptyl-benzoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 599 (M + H⁺)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(bicyclo[2.2.1]hept-5-ene-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 517 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(5-methyl-3-phenyl-isoxazole-4-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 582 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-tetradecanoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 607 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3,3-dimethyl-buteryl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 495 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenoxyacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 531 (M + H⁺)

5 Acetic acid 2-oxo-1-phenyl-2-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-ethyl ester

MS (CI): 573 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophene-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 507 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2,5,7-tetramethyl-1-oxoindane-4-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

15 MS (CI): 611 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-octanoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 523 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-octadec-9-enoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 661 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(quinoxaline-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 553 (M + H⁺)

30 4-Oxo-4-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-butyric acid methyl ester

MS (CI): 511 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(biphenyl-4-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 577 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pentanoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 481 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-isobutyryl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 467 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-decanoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 551 (M + H⁺)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-octadecanoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 663 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-hexanoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 495 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-phenyl-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 529 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclohexanecarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 507 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclobutanecarbonyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 479 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-ethyl-hexanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 523 (M + H⁺)

3-Oxo-3-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-propionic acid methyl ester

MS (CI): 497 (M + H⁺)

5-Oxo-5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-pentanoic acid methyl ester

15 MS (CI): 525 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-chloro-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 487 (M + H⁺)

20

5-Oxo-5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-pentanoic acid ethyl ester

MS (CI): 539 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(3-methoxy-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 545 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

30 MS (CI): 521 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 4.68 and 4.60 (s, 2H); 3.97 (s, 2H); 3.80 and 3.69 (t, 2H); 2.71 (m, 2H).

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-butyryl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 467 (M + H⁺)

5 4-Oxo-4-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-butyric acid methyl ester

MS (CI): 511 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-octadec-11-enoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 661 (M + H⁺)

METHOD B

15 Polymer bound EDC

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20 gm, 0.104 mol) was partitioned between 400 ml methylene chloride, 200 ml water, and 100 ml concentrated ammonium hydroxide. The aqueous layer was extracted with 2 x 100 ml methylene chloride. The combined organic layers were washed with 100 ml 10% ammonium hydroxide solution, 100 ml water, dried over magnesium sulfate, filtered and concentrated under vacuum to a clear colorless oil. The oil was dissolved in 350 ml DMF, Merrifield resin (100 gm, 2%div, 200-400 mesh, 1.0 mmol/gm) was added and the stirred mixture was heated at 100°C for 16 hours. After cooling, the resin was filtered, washed with 2 x 200 ml DMF, 2 times 300 ml THF, and dried in a 50°C vacuum oven for 20 hours. IR 2131 cm⁻¹.

Reaction

Into a glass screw topped vial was placed 50 μ l of a 0.050M solution of the acid in 1,2-dichloroethane (2.5 μ mol), followed by 50 μ l of 0.050M compound II in 1,2-dichloroethane (2.5 μ mol), followed by 30 μ l 0.017M DMAP in 1,2-dichloroethane (0.5 μ mol), followed by 25 mg polymer bound 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (@1.0 μ mol/gm=25 μ mol). After shaking at 20°C for 16 hours, 10 μ l was removed and

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diluted to 100 μ l with methanol for RPHPLC and MS analysis. The polymer was removed by filtration and the filtrate was concentrated to dryness under vacuum.

Example 40

- 5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(naphthalen-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide was made by reacting compound II with naphthalene-2-ylacetic acid in the presence of polymer bound EDC as described in METHOD B above.

MS (CI): 565 (M + H⁺)

10

Examples 41-97

The following compounds were made by reacting compound II with the appropriate corresponding carboxylic acid in the presence of polymer bound EDC, according to methods analogous to that described in Example 40.

15

- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2-dimethyl-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 481 (M + H⁺)

20

- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,2-dimethyl-pentanoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 509 (M + H⁺)

25

- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-hydroxy-2-phenyl-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 545 (M + H⁺)

30

- 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-phenyl-buteryl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 543 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-4-oxo-pentanoyl)-
1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 509 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-ethyl-buteryl)-1,2,3,4-tetrahydro-
isoquinolin-6-yl]-amide

MS (CI): 495 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethoxyacetyl-1,2,3,4-tetrahydro-
isoquinolin-6-yl)-amide

MS (CI): 483 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-fluoro-phenyl)-acetyl]-
1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

15 MS (CI): 533 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenylthioacetyl-1,2,3,4-
tetrahydroisoquinolin-6-yl)-amide

MS (CI): 547 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzylthioacetyl-1,2,3,4-
tetrahydroisoquinolin-6-yl)-amide

MS (CI): 561 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-buteryl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 481 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-buteryl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 501 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-but-3-enoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 465 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-acetyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 536 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-oxo-2-thioxo-thiazolidin-3-yl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 570 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(pyridine-4-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

15 MS (CI): 502 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(quinoline-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 552 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-phenyl-cyclopentane-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 569 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(a-methoxy-phenyl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 545 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-2,2-dimethyl-propionyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 515 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyanoacetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 464 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-methoxyacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 469 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-chloro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 549 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethylthioacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

15 MS (CI): 499 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-phenyl-prop-2-ynoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 525 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-hydroxy-butyryl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 483 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(1H-indol-3-yl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 554 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-methyl-pyridine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 516 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(pyridin-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 516 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 4.67 (s, 2H); 3.99 (s, 2H); 3.77 (m, 2H); 2.76 and 2.65 (t, 2H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-nitro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 560 (M + H⁺)

10

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-diethylcarbamoyl-cyclohex-3-enecarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 604 (M + H⁺)

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(adamantane-1-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 559 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(3-chloro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

20

MS (CI): 549 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-diphenylacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 591 (M + H⁺)

25

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(2,4-dichloro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 583 (M + H⁺)

30

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-phthalimido-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 584 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(biphenyl-4-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 591 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-o-tolylacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 529 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-m-tolylacetyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 529 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-phenyl-but-3-enoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

15 MS (CI): 541 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(cyclopent-1-enyl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 505 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(3,4,5-trimethoxy-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 605 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(adamantan-1-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 573 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(9H-fluorene-9-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 589 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(3-trifluoromethyl-phenyl)-acetyl]-
1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 583 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-cyclohexane-
carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 521 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[2-(1,3-dioxo-1,3-dihydro-isoindol-
2-yl)-propionyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 598 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-methyl-2-oxo-pentanoyl)-
1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 509 (M + H⁺)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methoxy-cyclohexanecarbonyl)-
1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 537 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-hex-3-enoyl-1,2,3,4-tetrahydro-
isoquinolin-6-yl)-amide

MS (CI): 493 (M + H⁺)

25 2-{6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-
isoquinoline-2-carbonyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

MS (CI): 594 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(tetrahydro-furan-3-carbonyl)-
1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 495 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(a-oxo-thiophen-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 552 (M + NH₄⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-3-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 521 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(6-methoxy-3-oxo-indan-1-yl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 600 (M + 2)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-acetyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 536 (M + H⁺)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(bicyclo[2.2.1]hept-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 533 (M + H⁺)

Example 98

Compound II (200mg, 0.50mmol), picolinic acid (62mg, 0.60mmol) and EDCI (116mg, 0.60mmol) were mixed in 10ml methylene chloride for 14 hrs. Reaction was concentrated and purified by flash chromatography on silica gel (eluent: 70-100% EtOAc/Hex). The product was 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(pyridine-2-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide, 98% yield.

MS (CI): 502 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 4.81 and 4.69 (s, 2H); 3.92 and 3.73 (t, 2H); 2.83 (m, 2H).

METHOD C

Into a glass screw topped vial was placed 150 μl of a 0.020M solution of the isocyanate in 1,2-dichloroethane (3.0 μmol), followed by 83 μl of 0.030M 4'-

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trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide (compound II) in 1,2-dichloroethane (2.5 μ mol) After shaking at 20°C for 16 hours, 10 μ l was removed and diluted to 100 μ l with methanol for RPHPLC and MS analysis. The reaction was concentrated to dryness under vacuum.

5

Example 99

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenylamide was made as described in Method C by reacting compound II with phenyl isocyanate.

10 MS (CI): 516 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 4.56 (s, 2H); 3.66 (t, 2H); 2.77 (t, 2H).

Examples 100-103

The following compounds were made by reacting compound II with the appropriate corresponding isocyanate according to methods analogous to those described in Example 99.

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid hexylamide

20 MS (CI): 524 (M + H⁺)

{6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carbonyl}-amino)-acetic acid ethyl ester

MS (CI): 526 (M + H⁺)

25

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid benzylamide

MS (CI): 530 (M + H⁺)

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid [(R)-1-phenyl-ethyl]-amide

Note: Product made as described in Method C using compound II and (R)-(+)- α -methylbenzyl isocyanate.

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MS (CI): 544 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 5.06 (m, 1H); 4.66 (d, 1H); 4.46 (s, 2H); 3.56 (t, 2H); 2.78 (t, 2H); 1.52 (d, 3H).

5

Example 104

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid pyridin-2-ylamide was prepared by a method analogous to the procedure described in Ohsawa, A.; Arai, H.; Igeta, H. *Chem. Pharm. Bull.* **1980**, *28*, 3570.

10 23% yield

MS (CI): 517 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 4.60 (s, 2H); 3.69 (t, 2H); 2.86 (t, 2H).

METHOD D

15 Into a glass screw topped vial was placed 150 μ l of a 0.020M solution of the sulfonyl chloride in 1,2-dichloroethane (3.0 μ mol), followed by 83 μ l of 0.030M compound II in 1,2-dichloroethane (2.5 μ mol), followed by 25 mg polymer bound morpholinomethylpolystyrene(@2.5 mmol/gm = 62 μ mol). After shaking at 20°C for 16 hours, 10 μ l was removed and diluted to 100 μ l with methanol for RPHPLC and MS
20 analysis. The polymer was removed by filtration and the filtrate was concentrated to dryness under vacuum.

Example 105

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(naphthalene-1-sulfonyl)-1,2,3,4-
25 tetrahydroisoquinolin-6-yl]-amide was prepared by METHOD D reacting compound II with naphthalene-1-sulfonyl chloride.

MS (CI): 604 (M + NH₄⁺)

Examples 106-111

30 The following compounds were prepared by METHOD D as in Example 105, by reacting compound II with the appropriate corresponding sulfonyl chloride.

2-{6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-sulfonyl}-benzoic acid methyl ester

MS (CI): 595 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(propane-2-sulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] -amide

MS (CI): 520 (M + NH₄⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-propane-1-sulfonyl)-
10 1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 555 (M + NH₄⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(butane-1-sulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

15 MS (CI): 534 (M + NH₄⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-dimethylsulfamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 521 (M + NH₄⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-trifluoromethoxy-benzenesulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 638 (M + NH₄⁺)

25 Example 112

This example illustrates how to make a compound where the group in XYZ linking XYZ to the tetrahydroisoquinoline ring is thiocarbamoyl.

Into a glass screw topped vial was placed 150 μ l of a 0.020M solution of the thioisocyanate (cyclopropylthioisocyanate) in 1,2-dichloroethane (3.0 μ mol), followed by 83 μ l of 0.030M 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide in 1,2-dichloroethane (2.5 μ mol). After shaking at 20°C for 16 hours, 10 μ l was removed and diluted to 100 μ l with methanol for RPHPLC and MS analysis. The reaction was concentrated to dryness under vacuum, yielding 4'-

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trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclopropylthiocarbamoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

MS (CI): 496 (M + H⁺)

5

METHOD F

A solution of aldehyde (7.5 μ mol), compound II (5 μ mol), acetic acid (7.5 μ mol), and sodium triacetoxyborohydride (10 μ mol) in 300 μ l of 1,2-dichloroethane was shaken for 60 hr at room temperature. A 7.5 μ l sample was removed and diluted with 93 μ l of methanol for TLC and MS analysis. The remaining sample was evaporated to dryness
10 *in vacuo*. The crude solid was dissolved in 500 μ l of ethyl acetate and washed with 300 μ l of 5% sodium bicarbonate. The organic layer was concentrated to dryness under vacuum.

Example 113

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,6,6-trimethyl-cyclohex-2-enylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide was made as described in METHOD F by reacting compound II with 2,6,6-trimethylcyclohex-2-enyl aldehyde.

MS (CI): 533 (M + H⁺)

20

Examples 114-162

The following compounds were made as in Example 113 by METHOD F by reacting compound II with the appropriate corresponding aldehyde.

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclohex-3-enylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 491 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

30 MS (CI): 501 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-dimethylamino-benzyl)-
1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 530 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-methoxy-benzyl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 517 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-fluoro-benzyl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 505 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3,4-dichloro-benzyl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 555 (M + H⁺)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-isopropyl-benzyl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 529 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-biphenyl-4-ylmethyl-1,2,3,4-
tetrahydroisoquinolin-6-yl)-amide

MS (CI): 564 (M + 2)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-phenoxy-benzyl)-1,2,3,4-
tetrahydroisoquinolin-6-yl]-amide

MS (CI): 580 (M + 2)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-methoxy-naphthalen-1-
ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 568 (M + 2)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-naphthalen-1-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 538 (M + 2)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-methylthio-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 533 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(9-ethyl-9H-carbazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 605 (M + 2)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-tert-butyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 544 (M + 2)

20 3-{6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-cyclohexanecarboxylic acid ethyl ester

MS (CI): 566 (M + 2)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-tert-butylthio-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 576 (M + 2)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclohexylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 494 (M + 2)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-fluoro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 505 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzo[1,3]dioxol-5-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 531 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-naphthalen-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 538 (M + 2)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-methoxy-naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 568 (M + 2)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-benzyloxy-3-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 624 (M + 2)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1,3,4-trimethyl-cyclohex-3-enylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 533 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[2-(4-chloro-phenylthio)-benzyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 629 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,4-dichloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 555 (M + H⁺)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1,5a,6,9,9a,9b-hexahydro-4H-dibenzofuran-4a-ylmethyl)-1, 2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 585 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[4-(2-diethylamino-ethoxy)-benzyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide

MS (CI): 603 (M + 2)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-trifluoromethyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 555 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 531 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-benzyloxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 594 (M + 2)

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-phenoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 579 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-dimethylamino-naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 580 (M + H⁺)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-pyrrolidin-1-yl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 557 (M + 2)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 493 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.83 (s, 2H); 3.52 (s, 2H); 2.69 (m, 4H).

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-indol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 526 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-pyrrol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 476 (M + H⁺)

¹H NMR (300 MHz, DMSO) δ 3.54 (s, 2H); 3.43 (s, 2H); 2.72 (m, 2H); 2.60 (m, 2H).

10

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-furan-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 477 (M + H⁺)

15 ¹H NMR (250 MHz, DMSO) δ 3.65 (s, 2H); 3.47 (s, 2H); 2.71 (m, 2H); 2.65 (m, 2H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 598 (M + 2)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,5-dimethyl-1-phenyl-1H-pyrrol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 581 (M + 2)

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 582 (M + 2)

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzofuran-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 527 (M + H⁺)

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Acetic acid 5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-furan-2-ylmethyl ester

MS (CI): 549 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 5.02 (s, 2H); 3.70 (s, 2H); 3.60 (s, 2H); 2.83 (t, 2H);
5 2.75 (t, 2H); 2.07 (s, 3H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 507 (M + H⁺)

10

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-3-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

MS (CI): 493 (M + H⁺)

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-methyl-1H-indol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 540 (M + H⁺)

20 2-Methyl-5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-furan-3-carboxylic acid ethyl ester

MS (CI): 563 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,5-dimethoxy-tetrahydrofuran-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

25 MS (CI): 541 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-1H-indol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

MS (CI): 557 (M + NH₄⁺)

30

2-{6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-cyclopropanecarboxylic acid ethyl ester

MS (CI): 523 (M + H⁺)

METHOD G

The following compounds were made via reductive amination by methods analogous to the procedure described in Abdel-Magid, A.F.; Maryanoff, C.A.; Carson, K.G. *Tetrahedron Lett.* **1990**, *31*, 5595. This procedure is essentially the same as
5 METHOD F and employs sodium triacetoxyborohydride, except that certain modifications, generally in the choice of solvent and reaction temperature have been made, all modifications being noted for each compound. In addition, unless otherwise noted, 1.5-2 equivalents of carbonyl compound was used. For compounds made in this section, it is noted that the free base was isolated. For use in biological screens
10 the free base was, in most cases, converted to the mono-hydrochloride salt by conventional methods.

Example 163

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzyl-1,2,3,4-tetrahydro-
15 isoquinolin-6-yl)-amide was made by reacting compound II with benzaldehyde, using a method analogous to that described in Abdel-Magid et al. above, with the following modifications:

Solvent: DCE

56% yield

20 MS (CI): 487 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.62 (s, 2H); 3.46 (s, 2H); 2.74 (m, 2H); 2.63 (m, 2H).

Examples 164-193

The following compounds were made by reacting compound II with the
25 appropriate corresponding aldehyde using methods analogous to that disclosed in Abdel-Magid et al., with appropriate modifications noted.

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: THF

30 62% yield

MS (CI): 488 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 3.82 (s, 2H); 3.63 (s, 2H); 2.84 (m, 2H); 2.77 (m, 2H).

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-3-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: THF

5 MS (CI): 488 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-4-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: THF

10 MS (CI): 488 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-quinolin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: DCE

15 66% yield

MS (CI): 538 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 3.99 (s, 2H); 3.67 (s, 2H); 2.82 (s, 4H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-methyl-pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

63% yield

MS (CI): 502 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 3.79 (s, 2H); 3.63 (s, 2H); 2.81 (s, 2H); 2.76 (s, 2H); 2.55 (s, 3H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-bromo-pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

30 MS (CI): 568 (M + H⁺)

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-formyl-pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

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Solvent: DCE; 10 equiv. of aldehyde used

MS (CI): 516 (M + H⁺)

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-chloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 521 (M + H⁺)

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

69% yield

MS (CI): 521 (M + H⁺)

¹H NMR (300 MHz, DMSO) δ 3.64 (s, 2H); 3.47 (s, 2H); 2.74 (t, 2H); 2.64 (t, 2H).

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(4-chloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 521 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyrimidin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: Methylene chloride; 6 equiv. of aldehyde used

61% yield

25 MS (CI): 489 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.87 (s, 2H); 3.60 (s, 2H); 2.77 (m, 4H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-nitro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

30 Solvent: DCE

76% yield

MS (CI): 532 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 3.75 (s, 2H); 3.58 (s, 2H); 2.84 (t, 2H); 2.73 (t, 2H).

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 517 (M + H⁺)

5

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-trifluoromethyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 555 (M + H⁺)

10

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-cyano-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 512 (M + H⁺)

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-hydroxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 503 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3,5-dichloro-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 556 (M + H⁺)

25

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3,5-bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 622 (M + H⁺)

30

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Acetic acid 3-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-phenyl ester

Solvent: DCE

MS (CI): 545 (M + H⁺)

5

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-sulfamoyl-benzyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 566 (M + H⁺)

10

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: 7:3 THF:DCE

59% yield

15

MS (CI): 477 (M + H⁺)

¹H NMR (300 MHz, CDCl₃) δ 3.79 (s, 2H); 3.58 (s, 2H); 2.82 (m, 2H); 2.74 (m, 2H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-1H-pyrrol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

57% yield

MS (CI): 490 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 3.64 (s, 3H); 3.57 (s, 2H); 3.51 (s, 2H); 2.77 (t, 2H); 2.65 (t, 2H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-benzoimidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

83% yield

MS (CI): 527 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.89 (s, 2H); 3.58 (s, 2H); 2.76 (m, 4H).

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

66% yield

5 MS (CI): 477 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.56 (s, 2H); 3.46 (s, 2H); 2.72 (m, 2H); 2.63 (m, 2H).

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide

Solvent: DCE

38% yield

MS (CI): 494 (M + H⁺)

¹H NMR (250 MHz, DMSO) δ 3.99 (s, 2H); 3.64 (s, 2H); 2.76 (s, 4H).

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-benzo[b]thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: DCE

MS (CI): 557 (M + H⁺)

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: 7:3 THF:DCE

72% yield

25 MS (CI): 491 (M + H⁺)

¹H NMR (300 MHz, DMSO) δ 3.66 (s, 2H); 3.63 (s, 3H); 3.47 (s, 2H); 2.70 (m, 2H); 2.62 (m, 2H).

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-3H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: THF

MS (CI): 491 (M + H⁺)

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide

Solvent: EtOH; Temp: 70°C

42% yield

5 MS (CI): 478 (M + H⁺)

¹H NMR (250 MHz, CDCl₃) δ 3.87(s, 2H); 3.63 (s, 2H); 2.79 (s, 4H).

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

10 Solvent: THF; 3 equiv. of aldehyde used

MS (CI): 411 (M + H⁺)

Example 194

This example demonstrates how to make a compound of formula II as illustrated
15 in Scheme 2. Numbers in parentheses with each title compound correspond to numbers in Scheme 2.

a. 2-(carboxy-5-nitro-phenyl)malonic acid dimethyl ester (2)

A solution of 2-chloro-4-nitrobenzoic acid (75g, 372mmol) in dimethyl malonate
20 (900mL) was sparged with nitrogen for 15 min. Sodium methoxide (48.3g, 894mmol) was added in one portion and the contents exothermed to 48°C. Fifteen minutes later, copper (I) bromide (5.4g, 37mmol) was added in one portion and the contents heated to 70°C for 24 hrs. The reaction was 70% complete by nmr, the contents heated to 85°C for 5 hrs to completely consume the 2-chloro-4-nitrobenzoic. Water (900mL) was
25 added to the cooled reaction followed by hexanes (900mL). The aqueous layer was separated, toluene (900mL) added, filtered through celite, and aqueous layer separated. Fresh toluene (1800mL) was added to the aqueous layer and the biphasic mixture acidified with 6N aqueous HCl (90mL). A white precipitate formed and the contents stirred for 18 hrs. The product was filtered off and dried to give a white solid (78.1g,
30 70%) mp=153°C.

¹H NMR (CD₃)₂SO δ 8.37 (d, J = 2 Hz, 1H), 8.30 (d, J = 1Hz, 2H), 5.82 (s, 1H), 3.83 (s, 6H).

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^{13}C NMR ($\text{CD}_3)_2\text{SO}$ δ 168.0, 167.3, 149.4, 137.1, 135.8, 132.5, 125.4, 123.7, 54.5, 53.4.

Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_8$: C, 48.49; H, 3.73; N, 4.71. Found: C, 48.27; H, 3.72; N, 4.76.

5

b. 2-carboxymethyl-4-nitro-benzoic acid (3)

To a solution of 2-(carboxy-5-nitro-phenyl)malonic acid dimethyl ester, (25.0g, 84mmol) in methanol (200mL), sodium hydroxide (5g, 125mmol) in water (200mL) was added. After 3 hrs the reaction was complete, the methanol removed under vacuum, contents cooled to 0°C and acidified with concentrated HCl (37mL). The aqueous layer was extracted twice with ethyl acetate (200mL then 100mL), the combined organic layers dried with magnesium sulfate, most of the solvent removed under vacuum, and methylene chloride (30mL) was then added. The white solid was filtered off and dried to give 19.3g of product as a white solid, mp= $180-82^\circ\text{C}$. IR(KBr) 3080, 3055, 2983, 1707, 1611, 1585, 1516, 1491, 1424, 1358, 1298, 1237 cm^{-1} .

^{13}C NMR ($\text{CD}_3)_2\text{SO}$ δ 172.3, 167.5, 149.2, 138.8, 137.3, 132.1, 127.2, 122.4, 39.8. Anal. Calcd for $\text{C}_9\text{H}_7\text{NO}_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 47.67; H, 3.19; N, 6.31.

20 c. 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol (4)

A THF (60mL) solution of 2-carboxymethyl-4-nitro-benzoic acid (3.0g, 13.3mmol) was treated with borane-THF complex (53.3mL, 53.3mmol) over 15 min at 0°C . The reaction was stirred for 18.5 hrs, quenched with THF/water (1:1, 30mL), water (20mL) added and the layers separated. The aqueous layer was reextracted with THF (30mL), the combined organic phase washed with brine, dried with magnesium sulfate, and solvent removed under vacuum to give the product as a white solid (2.05g, 78%) mp= $79-81^\circ\text{C}$.

IR(KBr) 3277, 3192, 2964, 2932, 1614, 1525, 1507, 1170, 1134, 1089, 1067 cm^{-1} .

^{13}C NMR ($\text{CD}_3)_2\text{SO}$ δ 149.1, 146.6, 139.2, 127.8, 124.3, 121.3, 61.2, 60.6, 34.9.

30 Anal. Calcd for $\text{C}_9\text{H}_{11}\text{NO}_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.54; H, 5.49; N, 7.07.

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c'. 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol (4), alternative procedure

A mixture of 2-carboxymethyl-4-nitro-benzoic acid (13g, 57.7mmol), acetic anhydride (5.45mL, 57.7mmol) and toluene (130mL) were heated to reflux for 5 hrs. The solvent was removed under vacuum to yield 6-nitro-isochroman-1,3-dione (compound (3a) in Scheme 2) as a yellow solid (10.51g, 88%). Borane tetrahydrofuran complex (35.6 mL, 1M in THF) was added dropwise over 40 min to a solution of 6-nitro-isochroman-1,3-dione (2g, 9.66mmol) in THF (40mL) at 0°C. The contents were stirred for 18 hrs at 25°C, cooled to 0°C, quenched with methanol (30mL), and stirred for 1 hr. The solvents were removed under vacuum, ethyl acetate (30mL) added and the organic phase washed with 10% aqueous hydrochloric acid. The aqueous acidic layer was reextracted with ethyl acetate (30mL), the combined organic layers dried with magnesium sulfate, and evaporated under vacuum until 2mL of ethyl acetate remained. This solution was filtered through silica gel washing with methylene chloride (30mL) to remove impurities. The silica gel was flushed with ethyl acetate, solvent removed under vacuum to give a solid which was slurried in methylene chloride and filtered to afford the diol as a white solid, 1.38g, 73%.

d. 6-nitro-1,2,3,4-tetrahydro-isoquinoline (5)

Methanesulfonyl chloride (0.9mL, 11.63mmol) was added dropwise over 10min to a solution of 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol (1.0g, 5.07mmol), triethyl amine (1.8mL, 12.91mmol), in methylene chloride (20mL). TLC showed complete reaction after 30 min. ¹H NMR (CD₃Cl) δ 8.17-11 (m, 2H), 7.65 (d, J = 9Hz, 1H), 5.36 (s, 2H), 4.49 (t, J = 6Hz, 2H), 3.25 (t, J = 6Hz, 2H), 3.08 (s, 3H), 2.98 (s, 3H). The reaction mixture was washed with 10% aqueous HCL, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried with magnesium sulfate, methylene chloride removed under vacuum and chased with THF (3X100mL). The product 1.9g was employed directly in the next reaction without further purification. Ammonia (50mL) was added to the dimesylate (1.9g) in THF (30mL) at -78°C. The contents were warmed to 24°C for 60 hrs, ammonia distilled out, and solvent removed under vacuum to give the crude product (786mg, 82%). Toluene was added and the solution was filtered through magnesium sulfate, and solvent removed under vacuum to yield 721mg (75%) of an amber oil.

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^1H NMR (CDCl_3) δ 7.97 (s, 1H), 7.95 (d, $J = 9\text{Hz}$, 1H), 7.15 (d, $J = 9\text{Hz}$, 1H), 4.07 (s, 2H), 3.15 (t, $J = 6\text{Hz}$, 2H), 2.89 (t, $J = 6\text{Hz}$, 2H), 1.98 (bs, 1H).

e. 6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (6)

5 To a solution of 6-nitro-1,2,3,4-tetrahydro-isoquinoline (840mg, 4.71mmol) in methylene chloride (17mL) containing triethylamine (0.72mL, 5.17mmol) was added BOC-anhydride (1.44mL, 6.26mmol). Saturated aqueous sodium bicarbonate was added 5 hr later, the phases separated, organic layer dried with magnesium sulfate, and solvent removed under vacuum to give the product as a pale white solid (1.2g, 10 92%). mp=138-41°C.

IR(KBr) 3056, 3018, 2982, 2935, 1734, 1684, 1612, 1522, 1399, 1236 cm^{-1} . ^1H NMR (CDCl_3) δ 8.04 (t, $J = 5\text{Hz}$, 1H), 8.01 (s, 1H), 7.26 (t, $J = 5\text{Hz}$, 1H), 4.65 (s, 2H), 3.68 (t, $J = 6\text{Hz}$, 2H), 2.93 (t, $J = 6\text{Hz}$, 2H), 1.49 (s, 9H).

15 f. 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (7)

The 6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (82mg, 0.29mmol) in THF (2mL) was hydrogenated with 5%Pt-C (50% water wet, 10mg) at 50psi for 5 hrs. The catalyst was filter off, solvent removed under vacuum and chromatographed on silica with ethyl acetate / hexanes to give 42mg (57%) of the 20 product.

IR(KBr) 3005, 2975, 2928, 1685, 1627, 1509, 1423, 1365, 1166 cm^{-1} .

^1H NMR (CDCl_3) δ 6.90 (d, $J = 6\text{Hz}$, 1H), 6.56 (d, $J = 6\text{Hz}$, 1H), 6.48 (s, 1H), 4.47 (s, 2H), 3.60 (m, $J = 6\text{Hz}$, 4H), 2.73 (t, $J = 6\text{Hz}$, 2H), 1.49 (s, 9H).

25 The product made as in Example 194 above can be reacted with 4'-trifluoromethyl-biphenyl-2-carboxylic acid as disclosed in Example 1 to afford the N-blocked compound II, then deblocked to yield compound II.

Example 195

30 This example demonstrates how to make compound II as shown in Scheme 3. Numbers in parentheses correspond to those in Scheme 3.

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a. 4'-trifluoromethyl-biphenyl-2-carbonyl chloride

A solution of 4'(trifluoromethyl)-2-biphenylcarboxylic acid (9.08g, 34mmol), thionyl chloride (12mL) and dimethylformamide (0.05mL) was heated to reflux for 2 hrs. The reaction was complete by NMR. Thionyl chloride was distilled by displacing with 5 toluene (56mL). Solvent was removed under vacuum to give the acid chloride as a white solid (9.46g, 97%).

^1H NMR (CDCl_3) δ 8.12 (dd, $J = 1\text{Hz}$, $J = 8\text{Hz}$, 1H), 7.70-7.37 (m, 7H). ^{13}C NMR CD_3Cl δ (CO) 168.

10 b. 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide (10)

Pt-C (50% water wet, 200mg) was added to a THF (40mL) solution of 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol (1.0g, 5mmol) and the reaction hydrogenated at 50psi for 2 hrs. NMR showed complete reaction to form 2-(5-amino-2-hydroxymethyl-15 phenyl)-ethanol (compound (9) in Scheme 3);

^1H NMR (CD_3Cl) δ 7.08 (d, $J = 2\text{Hz}$, 1H), 6.54-6.50 (m, 2H), 4.51 (s, 2H), 3.82 (t, $J = 6\text{Hz}$, 2H), 3.80-2.95 (bs, 4H), 2.84 (t, $J = 6\text{Hz}$, 2H).

The catalyst was filtered off, triethylamine (1.4mL, 10mmol) added, followed by dropwise addition of a THF (10mL) solution of the 4'-trifluoromethyl-biphenyl-2-carbonyl 20 chloride (1.44g, 5mmol) over 1hr. The contents were stirred for 24 hrs, the solvent removed under vacuum, and ethyl acetate (40mL) added. The organic phase was washed with water (2X40mL), dried with magnesium sulfate, solvent removed under vacuum, and chased with toluene (3X40mL). Upon removal of the solvent 2.11g a 25 white solid was obtained which was repulped in methylene chloride (21mL) for 18 hrs, the product filtered off, and dried to give the title product as a white solid 1.71g (81%).

^1H NMR ($\text{CD}_3)_2\text{SO}$ δ 10.22 (s, 1H), 7.73 (d, $J = 8\text{Hz}$, 2H), 7.62-7.28 (m, 8H), 7.20 (d, $J = 8\text{Hz}$, 1H), 4.96 (bs, 1H), 4.69 (bs, 1H), 4.43 (s, 2H), 3.51 (t, $J = 7\text{Hz}$, 2H), 2.67 (t, $J = 7\text{Hz}$, 2H).

30 IR(KBr) 3264, 3232, 31278, 3124, 3106, 2956, 2928, 1649, 1613, 1533, 1328, 1129 cm^{-1} .

-70-

^{13}C NMR (CD_3) $_2\text{SO}$ δ (amide CO) 167.7, aliphatic carbons 62.3, 61.1, 36.0. Anal. Calcd for $\text{C}_{23}\text{F}_3\text{H}_{20}\text{NO}_3$: C, 66.50; H, 4.85; N, 3.37. Found: C, 66.29; H, 4.79; N, 3.27.

5 c.4'-trifluoromethyl-biphenyl-2-carboxylic acid(1,2,3,4-tetrahydroisoquinolin-6-yl)-amide (compound II).

Methanesulfonyl chloride (0.085mL) was added to a 0°C solution of 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide (214mg, 0.51mmol) and triethylamine (0.18mL) in THF (8.5mL). TLC
10 showed complete reaction after 30 min. The contents were cooled to -78°C and ammonia was added and the contents stirred for 18 hrs at 25°C. The solvents were removed under vacuum, methylene chloride (10mL) and aqueous 1N aqueous HCl added and the contents stirred for 1 hr. The phases were separated and the aqueous phase made alkaline with aqueous sodium hydroxide to a pH of 12. The organic phase
15 was extracted with methylene chloride (4X10mL), solvent removed under vacuum to give a white solid 108mg which was chromatographed on silica eluting with 5% methanol/methylene chloride with 0.5% ammonium hydroxide. The product was obtained as a white solid (40mg, 20%).

^1H NMR (CDCl_3) δ 7.76-6.83 (m, 11H), 3.89 (s, 2H), 3.52 (d, J = 7Hz, 0.5H),
20 3.04 (t, J = 6Hz, 2H), 2.74 (m, 0.5H), 2.66 (t, J = 7Hz, 2H), 2.27 (s, 1H).

^{13}C NMR CD_3Cl δ (aliphatic carbons only) 47.8, 43.6, 29.1.

Examples 196-197 demonstrate how to make compounds according to the invention as illustrated in Scheme 3.

25

Example 196

4'-trifluoromethyl-biphenyl-2-carboxylic acid (2-benzyl-1,2,3,4-tetrahydroisoquinolin-6yl)-amide

Methanesulfonyl chloride (0.041mL) was added to a 0°C solution of 4'-
30 trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide (100mg, 0.24mmol) and triethylamine (0.084mL) in THF (2mL). TLC showed complete reaction after 30 min. Benzylamine (0.132mL) was added and the contents stirred for 18 hrs at 25°C and 60 hrs at 50°C. The solvent was removed under

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vacuum, the residue dissolved in methylene chloride (15mL), washed with pH9 buffer, phases separated, and the organic phase dried with magnesium sulfate. Removal of the solvent under vacuum gave the crude product as a white solid (204mg), which was repulped in CDCl_3 filtered off and dried to give the product as a white solid (46mg, 39%). mp=230-32°C.

^1H NMR ($\text{CD}_3)_2\text{SO}$ δ 7.73 (d, J = 8Hz, 2H), 7.60-7.23 (m, 12H), 7.17 (d, J = 8Hz, 1H), 6.87 (d, J = 8Hz, 1H), 3.60 (s, 2H), 3.43 (s, 2H), 2.71 (m, 2H), 2.62 (m, 2H).

Anal. Calcd for $\text{C}_{30}\text{F}_3\text{H}_{25}\text{N}_2\text{O}$: C, 74.06; H, 5.18; N, 5.76. Found: C, 74.08; H, 5.38; N, 5.76.

10

Example 197

4'-trifluoromethyl-biphenyl-2-carboxylic acid (2-allyl-1,2,3,4-tetrahydroisoquinolin-6yl)-amide

Methanesulfonyl chloride (0.041mL, 0.53mmol) was added dropwise to a THF (2mL) solution of triethylamine (0.084mL, 0.60mmol) and 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide (0.1g, 0.24mmol) at -20°C. Fifteen minutes after the addition was complete allylamine (0.09mL, 1.2mmol) was added, the contents stirred at 25°C for 18 hrs and then 70 hrs at 60°C. The solvent was removed under vacuum, methylene chloride (10mL) added and organic phase washed with pH12 water (10mL). The organic solvent was removed under vacuum to afford 281mg of crude product. This material was chromatographed on silica eluting with 10% methanol/methylene chloride to afford the product as a white solid (91mg, 87%).

^1H NMR (CDCl_3) δ 7.80 (d, J = 8Hz, 1H), 7.68 (d, J = 8Hz, 2H), 7.60-7.42 (m, 5H), 6.93-6.83 (m, 3H), 6.00-5.86 (m, 1H), 5.27-5.17 (m, 2H), 3.55 (s, 2H), 3.15 (d, J = 7Hz, 2H), 2.83 (t, J = 6Hz, 2H), 2.69 (t, J = 6Hz, 2H), 1.66 (bs, 1H).

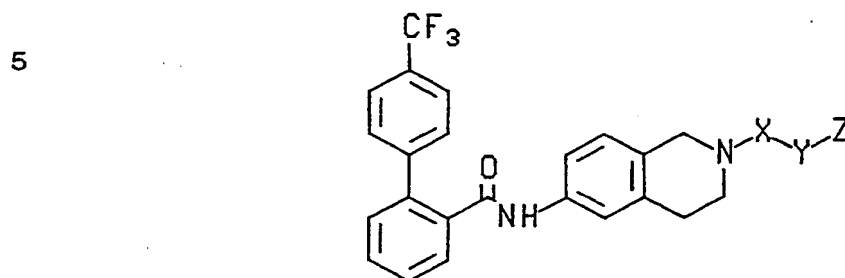
^{13}C NMR CD_3Cl δ (aliphatic carbons only) 61.4, 55.6, 50.3, 29.1.

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CLAIMS

What is claimed is:

1. A compound of formula I



wherein

X is CH₂, CO, CS, or SO₂;

Y is selected from:

a direct link,

15 aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be mono-substituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl,

NH, and O,

provided that if X is CH₂, Y is a direct link;

20 Z is selected from the following groups:

(1) H, halo, cyano,

(2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,

(3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino,

25 provided that Y is not O or NH,

(4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,

(5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,

30 (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms

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independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic,

provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

- 5 wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl;
- 10 and pharmaceutically acceptable salts thereof.

2. A compound as defined in claim 1, and pharmaceutically acceptable salts thereof,
- 15 wherein:

X is CH₂, CO, or SO₂;

Y is selected from:

a direct link, NH,

- (C₁-C₁₀)alkylene and (C₂-C₁₀)alkenylene, either of which may be substituted with
- 20 phenyl,
- provided that if X is CH₂, Y is a direct link,

Z is selected from the following groups:

- (1) H,
- (2) (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio,
- 25 (3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino,
- provided that Y is not NH,

(4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl,

(5) (C₆-C₁₀)aryloxy,

- (6) heterocyclyl selected from the group consisting of five- and six-
- 30 membered heterocyclic radicals, which may be saturated, partially unsaturated, or aromatic, and the fused benz derivatives thereof, wherein said radicals may contain a total of from 1 to 3 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur,

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wherein, when Z contains one or more rings, said rings may each independently bear 0 to 3 substituents independently selected from halo, hydroxy, nitro, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, and (C₁-C₁₀)acyloxy.

5

3. A compound as defined in claim 2, and pharmaceutically acceptable salts thereof, wherein X is methylene, Y is a direct link, and Z is selected from (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, and (C₄-C₈)cycloalkenyl each of which may bear 0 to 3 of the said independent substituents.

10

4. A compound as defined in claim 2, and pharmaceutically acceptable salts thereof, wherein X is methylene or CO, Y is a direct link, and Z is heterocyclyl selected from thiophenyl, pyrrolidinyl, pyrrolyl, furanyl, thiazolyl, isoxazolyl, imidazolyl, 1,2,4-triazolyl, pyridyl, pyrimidinyl, and the fused bicyclic (ortho) benz derivatives thereof, each of
15 which may bear 0 to 3 of the said independent substituents.

5. A compound as defined in claim 2, and pharmaceutically acceptable salts thereof, wherein

X is CH₂ or CO;

20 Y is a direct link;

Z is

H, unsubstituted vinyl, phenyl,

imidazolyl, thiazolyl, thiophenyl, 1,2,4-triazolyl, pyridinyl, and pyrimidinyl.

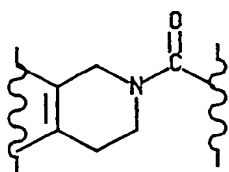
25 6. A compound as defined in claim 5, wherein X is CO.

7. A compound as defined in claim 5, wherein X is CH₂.

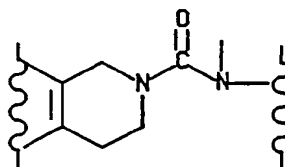
8. A compound as defined in claim 1, wherein the linking group formed by the ring
30 nitrogen of the 1,2,3,4-tetra-hydroisoquinoline ring shown in formula I taken together with the group in -XYZ which links the said XYZ moiety to the said ring nitrogen is selected from:

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5

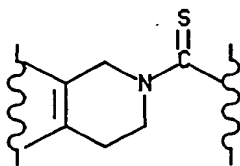


Amides

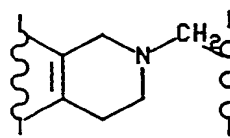


Ureas

10

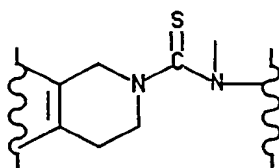


Thioamides

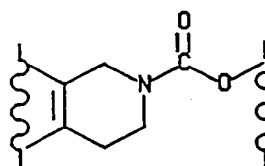


N-alkyls

15

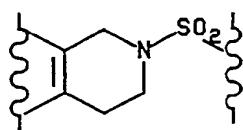


Thioureas



Carbamate

20



Sulfonamides

9. A compound as defined in claim 8, wherein said linking group is an amide.

10. A compound as defined in claim 9, selected from the group consisting of:

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenyl-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-phenoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pentanoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclobutane-carbonyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-butyryl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

15 4'-Trifluoromethyl-biphenyl-2-carboxylic acid {2-[(4-fluoro-phenyl)-acetyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-methyl-butyryl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-but-3-enoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-methoxy-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-ethylthio-acetyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

30 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(6-diethyl-carbamoyl-cyclohex-3-enecarbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(cyclopent-1-enyl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-hex-3-enoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(tetrahydrofuran-3-carbonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-3-yl-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide, and

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(pyridine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide.

11. A compound as defined in claim 8, wherein said linking group is a urea.

15 12. A compound as defined in claim 11, selected from the group consisting of:

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid phenylamide,

20 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid hexylamide,

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-di-hydro-1H-isoquinoline-2-carboxylic acid benzylamide,

25 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid [(R)-1-phenyl-ethyl]-amide, and

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid pyridin-2-ylamide.

30

13. A compound as defined in claim 8, wherein said linking group is a sulfonamide.

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14. A compound as defined in claim 13, selected from the group consisting of:

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(propane-2-sulfonyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

5 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-dimethylsulfamoyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide, and

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2-trifluoromethoxy-benzenesulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide.

10

15. A compound as defined in claim 8, wherein said linking group is a thiourea.

16. A compound as defined in claim 15, which is 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-cyclopropylthiocarbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide.

15

17. A compound as defined in claim 8, wherein said linking group is a N-alkyl.

18. A compound as defined in claim 17, selected from the group consisting of:

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,6,6-trimethyl-cyclohex-2-enylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

20

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,4-dichloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1,5a,6,9,9a,9b-hexahydro-4H-dibenzofuran-4a-ylmethyl)-1, 2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

30

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-pyrrol-2-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-furan-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

Acetic acid 5-{6-[(4'-trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-ylmethyl}-furan-2-ylmethyl ester,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiophen-3-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(2,5-dimethoxy-tetrahydro-furan-3-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-benzyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

15

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

20 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-quinolin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-chloro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

25 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyrimidin-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(3-nitro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]-amide,

30

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-pyrrol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-benzoimidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1-methyl-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide, and

4'-trifluoromethyl-biphenyl-2-carboxylic acid [(2-allyl)-1,2,3,4-tetrahydroisoquinoline-6-yl] amide.

19. A compound as defined in claim 8, wherein said linking group is a carbamate.

20. A compound as defined in claim 19, which is 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester.

21. A compound as defined in claim 8, wherein said linking group is a thioamide.

22. A compound as defined in claim 8, selected from the group consisting of:

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide,

6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ([R]-1-phenyl-ethyl)-amide,

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4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-
5 tetrahydroisoquinolin-6-yl]-amide,

4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, and

10 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide.

23. A compound as defined in claim 22, which is 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(thiophen-2-yl-acetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide.

15

24. A compound as defined in claim 22, which is 6-[(4'-Trifluoromethyl-biphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid (1-phenyl-ethyl)-amide.

25. A compound as defined in claim 22, which is 4'-Trifluoromethyl-biphenyl-2-
20 carboxylic acid (2-pyridin-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide.

26. A compound as defined in claim 22, which is 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-imidazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide.

25 27. A compound as defined in claim 22, which is 4'-Trifluoromethyl-biphenyl-2-carboxylic acid (2-thiazol-2-ylmethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide.

28. A compound as defined in claim 22, which is 4'-Trifluoromethyl-biphenyl-2-carboxylic acid [2-(1H-[1,2,4]triazol-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-
30 6-yl]-amide.

29. A pharmaceutical composition comprising a compound of formula I as defined in claim 1, and a pharmaceutically acceptable carrier.

SUBSTITUTE SHEET (RULE 26)

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30. A composition as defined in claim 29, further comprising an additional lipid-lowering agent.
31. A method of treating a condition selected from atherosclerosis, pancreatitis, obesity, hypercholesteremia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising administering to a mammal in need of such treatment an amount of a compound of formula I as defined in claim 1 sufficient to decrease the secretion of apolipoprotein B.
32. A method as defined in claim 31, wherein said condition is selected from atherosclerosis, pancreatitis, obesity, and diabetes.
33. A method as defined in claim 32, wherein said condition is atherosclerosis.
34. A method of decreasing apoB secretion in a mammal, comprising administering to said mammal an apoB secretion decreasing amount of a compound of formula I as defined in claim 1.
35. A compound selected from:
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide,
- 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol,
- 6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester,
- 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, and
- 2-(5-amino-2-hydroxymethyl-phenyl)-ethanol.
36. A compound as defined in claim 35, selected from:
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, and
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide.

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37. A compound as defined in claim 35, which is 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester.

AMENDED CLAIMS

[received by the International Bureau on 11 June 1996 (11.06.96);
original claim 37 cancelled;
original claim 35 amended (1 page)]

30. A composition as defined in claim 29, further comprising an additional lipid-lowering agent.
31. A method of treating a condition selected from atherosclerosis, pancreatitis, obesity, hypercholesteremia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising administering to a mammal in need of such treatment an amount of a compound of formula I as defined in claim 1 sufficient to decrease the secretion of apolipoprotein B.
32. A method as defined in claim 31, wherein said condition is selected from atherosclerosis, pancreatitis, obesity, and diabetes.
33. A method as defined in claim 32, wherein said condition is atherosclerosis.
34. A method of decreasing apoB secretion in a mammal, comprising administering to said mammal an apoB secretion decreasing amount of a compound of formula I as defined in claim 1.
35. A compound selected from:
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide,
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide,
- 2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol,
- 6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, and
- 2-(5-amino-2-hydroxymethyl-phenyl)-ethanol.
36. A compound as defined in claim 35, selected from:
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, and
- 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxymethyl-phenyl]-amide.

INTERNATIONAL SEARCH REPORT

Int. .onal Application No

PCT/IB 95/00448

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D217/04	C07D217/06	C07D405/06	C07D413/06	C07D409/06
	C07D401/06	C07D417/06	C07D217/08	C07D401/10	C07C233/75
	C07D217/02	C07C205/19	C07C215/68	A61K31/47	A61K31/495
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
IPC 6 C07D C07C					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	EP-A-0 635 492 (ELI LILLY AND COMPANY) 25 January 1995 see page 47, scheme 20, compound 143 ---				35,37
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 18, no. 12, December 1975 pages 1227-1231, MATHISON I.W. & TIDWELL R.R. 'Structure-activity relationships of antiarrhythmic 6-substituted decahydroisoquinolines' see compound 16, tables I and II ---				1-30, 35-37
A	US-A-4 022 900 (MATHISON I.W.) 10 May 1977 see the whole document --- -/--				1-30, 35-37
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family					
Date of the actual completion of the international search			Date of mailing of the international search report		
14 February 1996			14.03.96		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016			Authorized officer Hartrampf, G		

INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/IB 95/00448

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP-A-0 106 140 (THE WELLCOME FOUNDATION LIMITED) 25 April 1984 see the whole document ---	1-30, 35-37
A	EP-A-0 643 057 (BRISTOL-MYERS SQUIBB COMPANY) 15 March 1995 cited in the application see the whole document -----	1-30, 35-37

INTERNATIONAL SEARCH REPORT

Int. application No.

PCT/IB 95/00448

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 31-34 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 95/00448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BR-A- 9402916	11-04-95
		CA-A- 2128348	23-01-95
		CN-A- 1108248	13-09-95
		CZ-A- 9401740	13-09-95
		FI-A- 943478	23-01-95
		HU-A- 70397	30-10-95
		NO-A- 942734	23-01-95
		PL-A- 304388	23-01-95
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		JP-A- 59067246	16-04-84
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		CZ-A- 9402124	16-08-95
		FI-A- 944048	04-03-95
		HU-A- 70613	30-10-95
		JP-A- 7165712	27-06-95
		NO-A- 943260	06-03-95
		PL-A- 304883	06-03-95